FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

NDA 204-804
Singulair® Allergy
(montelukast sodium)
10 mg tablets

Meeting Date: May 2, 2014

Presented to the Nonprescription Drugs Advisory Committee

Merck Consumer Care

Available for Public Disclosure Without Redaction

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(montelukast sodium) 10 mg tablets

Reader's Guide to Briefing Document

Section 1 - Executive Summary: This section provides a condensed summarization of the key elements of the switch rationale ("partial switch") and the development program supporting the proposed Rx-to-OTC Switch of Singulair Allergy. Links are provided to the subsequent sections which provide more comprehensive details of any given topic.

Section 2 - Allergic Rhinitis Condition & Current OTC Treatment Options: An overview is provided on the high prevalence of allergy in the U.S. and the currently available OTC choices. Also included is an overview of current treatment behaviors where frequent brand switching is reported because consumers are not fully satisfied with their options. Singulair Allergy would offer a new choice to these consumers. The unique properties of Singulair Allergy are explained, highlighting the non-sedating, 24-hour relief from the major allergy symptoms, including nasal congestion and itchy/watery eyes.

Section 3 - Approval History, Mechanism of Action and Pharmacology: This section outlines the Rx approval history of montelukast for its different indications, including seasonal and perennial allergic rhinitis. Although Rx Singulair 10 mg is approved for ages 15 and up, and at lower doses for pediatric populations, this partial OTC switch is only for allergy, for adults 18 years and older. This strategy is consistent with other first-in-class switches, and pediatric allergy products could potentially be switched in the future. The mechanism of action and pharmacology of montelukast are also reviewed here.

Section 4 - Review of Clinical Efficacy: The efficacy of Singulair in allergy has been established in multiple clinical studies leading to approval of the prescription product, and the results of those studies are reviewed here. Particular attention is paid to the ocular symptom endpoints (specifically "itchy/watery" eyes), which were significantly positive in two of three pivotal seasonal studies and their pooled analysis. Those symptoms are not listed in the Rx label because they had been pre-defined only as secondary endpoints. MSD Consumer Care, Inc. is requesting that itchy/watery eyes relief be included in the list of symptoms treated in the OTC label because this information is based on clinically relevant efficacy that will be useful to consumers.

Section 5 - Review of Safety: Safety analyses from controlled clinical trials and from post-marketing reports and other databases are summarized here. Singulair is well-tolerated and has demonstrated a favorable safety profile with a low incidence of adverse events (AEs), comparable to placebo in clinical trials, and no clinically important drug-drug interactions. Montelukast has also been studied at doses as high as 90 times the therapeutic dose with a safety profile similar to the 10 mg tablet, which is another important factor for an OTC product. Since market introduction in

1997, spontaneously reported AEs have been collected and incorporated into Rx labeling, including neuropsychiatric events. Although, a biologic mechanism has not been identified, it is not possible to rule out an association of these uncommon events to leukotriene-modifying agents such as montelukast. Therefore, current Rx and proposed OTC labeling includes warnings in this regard. The overall benefit/risk profile of Singulair is favorable.

Sections 6, 7 & 8 – Topics Relevant to Switch, Labeling, and the OTC Development Program: These sections identify the key areas of the proposed OTC Drug Facts label that would differ from standard class labeling for OTC allergy products like antihistamines. The main areas of focus are the adult-only population, directives not to use for self-management of asthma, and warnings regarding unexpected changes in behavior, mood or sleep. Three studies in over 1600 subjects were conducted according to FDA Guidelines to measure label comprehension and self-selection. These studies reached or exceeded nearly all predefined thresholds for success, demonstrating that general and targeted populations, such as people with asthma or low literacy skills can appropriately understand label directions and warnings and can correctly choose whether or not to use the Singular Allergy product.

Sections 9 & 10 – Benefit/Risk Assessment and Overall Conclusions: These sections place all of the efficacy, safety and consumer research data into the context of the overall benefits and incremental risks of OTC status. The benefits of convenient access to a product with a unique mechanism, providing multi-symptom relief, outweigh the risks of off-label use. The well-understood Drug Facts label directs not to use to treat asthma and provides warnings regarding unexpected behavior or mood-related changes. Therefore, Singulair Allergy is an appropriate candidate for OTC availability.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAPCC	American Association of Poison Control Centers
AERS	Adverse Event Reporting System
AEs	Adverse Events
AR	Allergic Rhinitis
AUC	Area Under the Curve
BRAEs	Behavior-Related Adverse Events
CI	Confidence Interval
CIL	Consumer Information Leaflet
C_{max}	Peak serum concentration
CYP	Cytochrome P
$CysLT_1$	Cysteinyl Leukotriene Type-1
CysLTs	Cysteinyl Leukotrienes
DAWN	Drug Abuse Warning Network
ED	Emergency Department
EIB	Exercise Induced Bronchoconstriction
EPR	Expert Panel Review
FCT	Film-Coated Tablet
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in One Second
GEoAR	Global Evaluation of AR
HCP	Healthcare Provider
ICSR	Individual Case Safety Report
IgE	Immunoglobin-E
IMPACT	IMProving Asthma Control Trial
IND	Investigational New Drug
LB	Lower Bound (of the 95% CI)
MARRS	Merck Adverse Event Reporting and Review System
MCC	Merck Consumer Care
NDA	New Drug Application
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over-the-Counter
PAR	Perennial AR
PE	Phenylephrine
PEF	Peak Expiratory Flow
PSE	Pseudoephedrine
PSRAEs	Possibly Suicidality-Related Adverse Events
PT	Preferred Term
PTY	Patient-Treatment Year
QoL	Quality of Life
REALM	Rapid Estimate of Adult Literacy in Medicine
RQoL	Rhinoconjunctivitis Quality of Life

Rx	Prescription
Rx-to-OTC	Prescription to Over-the-Counter
SAE	Serious Adverse Event
SAR	Seasonal AR
SOC	System Organ Class
SOLID	Singulair OTC Label Interpretation and Decisions
T_{max}	Time to reach peak serum concentration
WHO	World Health Organization

1.0 EXECUTIVE SUMMARY

1.1 Overview

Allergic Rhinitis (AR) is one of the most common conditions affecting the U.S. population. AR is a significant medical problem even though a large number of medical treatments are available, both by prescription (Rx) and over-the-counter (OTC).

Prescription Singulair (hereafter referred to as 'Rx Singulair') is a leukotriene receptor antagonist that is currently (as of March 2014) available in more than 100 countries for allergy and asthma indications. The 10 mg film-coated tablet (FCT) is approved for patients 15 years of age and older. Additional dosage forms (4 and 5 mg chewable tablets and 4 mg oral granules) are approved for younger patients. In the U.S., Rx Singulair is approved for the following indications and patient populations: (see also the current Prescribing Information in **Appendix 1**)

- Prophylaxis and chronic treatment of asthma (initially approved in 1998), currently approved in patients 12 months and older;
- Relief of symptoms of AR: seasonal AR (SAR) in patients 2 years of age and older (approved in 2002), and perennial AR (PAR) in patients 6 months of age and older (approved in 2005);
- Acute prevention of exercise-induced bronchoconstriction (EIB) (initially approved in 2007), currently approved in patients 6 years of age and older.

In addition to montelukast, there are currently two other leukotriene modifying agents available in the U.S. for the treatment of asthma: zileuton and zafirlukast. Montelukast, however, has the distinction of being the only leukotriene modifying agent approved in the U.S. for AR.

MSD Consumer Care, Inc., operating under the trade name Merck Consumer Care, Inc. (MCC), has submitted a New Drug Application (NDA 204-804), for the partial OTC switch of Singulair (montelukast sodium) 10 mg FCT for AR, hereafter referred to as 'Singulair Allergy.'

MCC is proposing the prescription to over-the-counter (Rx-to-OTC) switch of only the 10 mg FCT for the treatment of AR in adults 18 years of age and older. The asthma indications will remain Rx making this a partial switch application. The potential for consumer confusion between the Rx asthma and OTC AR products was considered extensively, and is discussed at length in this application.

In addition, the pediatric age groups will also remain Rx. The decision to switch only the adult indication in this application was discussed with the FDA during the Pre-NDA meeting, and is consistent with other first-in-class Rx-to-OTC switches including Proton Pump Inhibitors (e.g., Prilosec OTC) and the weight loss aid Alli, where higher doses, pediatric uses, or more medically serious indications remain Rx

for a variety of reasons. The 10 mg strength of Rx Singulair is currently approved down to age 15 years, but because 15 years is an unusual age cut-off for the OTC market, MCC made the decision to develop the label for adults 18 years and older for this OTC switch. MCC believes that maintaining age cutoff consistency with other products in the OTC market can help to avoid consumer confusion. This will also provide the opportunity to gain experience with the new product in the OTC environment marketplace prior to expanding it to the pediatric population. With completion of additional label development studies required by the FDA for the pediatric doses, the product could be expanded to ages 15-17, and products at lower doses for younger ages could be added in the future.

MCC has also requested that the OTC label include ocular symptom relief (specifically itchy/watery eyes), although they are not listed in the Rx label. This will give consumers the most appropriate and complete information about the efficacy of Singulair Allergy, as montelukast has been shown to improve these symptoms during its development program. AR patients generally suffer from a constellation of symptoms that are not only limited to the nose. Although sneezing, nasal itching, runny nose, and nasal congestion are important symptoms of AR, others including itchy/watery eyes, have been identified to be just as bothersome for AR patients as nasal symptoms.[1]

The efficacy of Rx Singulair for relief of symptoms of AR was well demonstrated in the large clinical development program that supported the U.S. approvals for both SAR and PAR. In the current Rx labeling, efficacy is described on the primary endpoint of Daytime Nasal Symptoms (which includes the symptoms of nasal congestion, rhinorrhea, nasal itching, sneezing). Although many other secondary endpoints in this development program demonstrated efficacy, these are not reflected in the label (consistent with the current emphasis on the primary endpoint that is outlined in the current FDA Draft Guidance for Industry – Allergic Rhinitis: Clinical Development Programs for Drug Products issued in April 2000).[2]

Nevertheless, eye symptoms associated with AR are well understood by consumers and are described in the current labeling for many products now available OTC for AR. To support description of eye symptoms in the OTC label for Singulair Allergy, the Rx-to-OTC switch NDA included efficacy data from the AR clinical development program, with attention both to nasal symptoms and ocular symptoms. In this briefing document, efficacy data from the Rx clinical development program, including data supporting a claim for “itchy/watery eyes,” are provided in **Section 4.0**.

Although Singulair Allergy would be a first-in-class Rx-to-OTC switch, AR is a well-established OTC treatment category that consumers can self-diagnose and self-treat. The safety profile of Rx Singulair is supported by extensive safety data from more than 100 controlled clinical trials (for all indications) in which 20,000 plus patients were exposed to montelukast (**Section 5.0**). Additionally, there are more than 16 years of post-marketing safety experience since the first global Rx approval for asthma (in Mexico, July 31, 1997). The extensive post-marketing safety data

(from market introduction to May 30, 2013) includes more than 24 billion drug units distributed globally, representing approximately 66 million patient-treatment years.*

The potential switch of Singulair Allergy would offer consumers the following distinct advantages:

- A new OTC AR treatment choice with a unique mechanism of action, as a leukotriene receptor antagonist; (**Section 2.3**)
- The only single-ingredient tablet available to provide non-sedating 24-hour relief of AR symptoms, including nasal congestion, an important benefit currently not provided by single ingredient antihistamines; (**Section 3.3**)
- No clinically important drug-drug or drug-food interactions associated with montelukast, making it safe to be taken with other medications and without regard to the timing of meals; (**Section 3.4**)
- Montelukast's pharmacologic profile [i.e., high affinity and specificity to the cysteinyl-leukotriene Type 1 ($CysLT_1$) receptor] allows montelukast to be administered to people who cannot take certain OTC decongestant drugs due to co-morbidities like hypertension, heart disease, diabetes or glaucoma; (**Sections 3.4** and **5.4**)
- Contrary to existing OTC anti-muscarinic AR medications, montelukast lacks any anticholinergic effects and lacks the stimulatory effects associated with adrenergic agents. (**Section 3.3**)

This briefing document focuses on a detailed review of:

- The development plan implemented to demonstrate OTC suitability, including three consumer label comprehension and self-selection studies; (**Section 8**)
- Ocular efficacy data from the original clinical development program for AR; (**Section 4.0**)
- Safety data from the original and supplemental NDAs (adult safety data only) (**Section 5.1**) and post-marketing safety (**Section 5.3**) from internal (**Section 5.3.2**) and external safety databases; (**Sections 5.3.3**)
- Discussion on benefits and potential risks associated with OTC availability of Singulair Allergy. (**Section 9.0**)

The briefing document also discusses the current AR landscape, approval history and pharmacology of montelukast and a review of the proposed OTC Drug Facts label.

* based on the assumption that each patient takes one tablet or oral granule sachet daily.

1.2 AR: Pathophysiology, Health Burden and Current Self-Management Treatment Options

AR is the fifth most prevalent chronic disease in the U.S.[3] Nearly 75 million Americans are affected by allergies.[4,5] The prevalence of AR in adults is about 10 to 30%.[1]

AR is a disorder of the upper airway induced by an immunoglobulin E (IgE)-mediated inflammation. Upon exposure to a relevant antigen, several inflammatory mediators including histamine, cysteinyl leukotrienes (CysLTs) and prostaglandins are released. These mediators lead to the emergence of symptoms of nasal congestion, rhinorrhea, sneezing, and nasal pruritus (itchy nose) as well as non-nasal symptoms such as eye itching and eye tearing, which have been identified to be nearly as bothersome to patients.[7]

Although not life threatening, AR is lifestyle-limiting and has a well-documented impact on health-related and overall quality of life measures. It negatively affects school and work performance, sleep, and social life regardless of gender, age, social or ethnic background.[8] In fact, 40% of people with allergies say their allergies have a moderate to significant impact on their quality of life and 38% report an even greater impact, saying they "cannot tolerate" the discomfort from their allergies.[9] Additionally, more than 90% of patients with moderate to severe AR report that symptoms affect their ability to conduct their daily activities and 80% report difficulty sleeping and, thus, experience increased fatigue during the data.[9,10] AR accounts for nearly 10 million missed or lost workdays each year.[11]

While the symptoms of AR are readily recognizable and their impact on patient quality of life is significant, it has been reported that nearly 1 in 4 people with allergies is not fully satisfied with their OTC choices and 75% report wanting additional OTC allergy treatment choices.[7] Consistent with this data, 35% of users of OTC allergy products report switching among products with different antihistamines or combination ingredients.[12,6]

Currently Available Self-Management Treatment Options for AR

Few people with AR seek care from a physician and most patients with allergies turn to OTC medications for self-treatment.[13] According to a 2013 survey by the Consumer Healthcare Products Association, 90% of people with AR self-treat their symptoms regularly or occasionally.[14] In addition, nearly 60% only use OTC medicines or herbal/homeopathic products for their symptoms. [12]

Currently approved OTC agents specifically indicated for the treatment of AR symptoms are summarized below, highlighting their benefits and limitations: **Oral H_1-antihistamines**: First-generation antihistamines are effective at relieving most symptoms of AR but high penetration into the central nervous system results in well-known sedative effects.[15] When using these products, users must use caution when driving or operating machinery and should avoid alcoholic beverages. First-

generation antihistamines are also non-selective and have anticholinergic effects that commonly result in dry mouth and, rarely, in serious cardiac dysrhythmias.[15]

Second-generation antihistamines have an improved adverse event profile versus the first generation but their use may be limited by drug-drug and/or drug-food interactions.[1,46]In addition, antihistamines do not relieve nasal congestion, which is reported to be the most common and bothersome symptom of AR.[1,13]

- **Combination Oral Antihistamines/Decongestants:** Pseudoephedrine (PSE) and phenylephrine (PE) are nasal decongestants frequently combined with antihistamines.

PSE is an effective nasal decongestant. Adverse events include nervousness, agitation, palpitations, and insomnia. As a result, the Drug Facts labels for nonprescription products containing PSE cautions users to consult a doctor before use if they have liver or kidney disease, heart disease, high blood pressure, thyroid disease, diabetes or trouble urinating due to an enlarged prostate gland.[16,17] PSE may be obtained only in small quantities from the pharmacist after the presentation of valid identification.

PE is another alpha-agonist decongestant frequently combined with antihistamines. It has a similar adverse event profile to PSE and has a short half-life, so its effect does not last long and dosing must be repeated every 4 hours.[18]

- **Intranasal Cromolyn**: This ingredient acts by stabilizing degranulation of mast cells leading to histamine release and has modest efficacy, and can be dosed 4-6 times daily. Also, it is recommended to initiate therapy one week in advance of anticipated contact with seasonal allergens.[19]

- **Intranasal Corticosteroids:** The most recently approved OTC AR medication is triamcinolone acetonide. Intranasal corticosteroids are an effective treatment for reducing inflammation of the nasal mucosa, but it may take up to one week of daily use to feel the most symptom relief. Nasal sprays are not the most preferred dosage form for the treatment of allergies and may be rejected by some people.[20]

All of these currently available OTC treatments exert their effect through a variety of actions but none act directly on CysLT receptors, the targeted mechanism of action of Singulair Allergy.

Therefore, Singulair Allergy would be the only single-ingredient tablet to offer many of the same treatment benefits as existing OTC products for AR, plus the relief of nasal congestion, with less of the limitations present in the category today.

1.3 Mechanism of Action and Pharmacology

Montelukast sodium is an antagonist of the $CysLT_1$ receptor, and it is the only product with this mechanism of action that is approved in the U.S. for relief of symptoms of AR. It binds with high affinity and selectivity to $CysLT_1$ receptor and thereby inhibits physiologic actions of CysLTs at the $CysLT_1$ receptor without agonist activity. Its favorable safety profile may be due to its specific blockade of $CysLT_1$ receptors and the apparent lack of a meaningful role for $CysLT_1$ receptor occupancy in normal physiologic functions.

The pharmacology of montelukast has been well characterized and supports ease of use by consumers in an OTC environment:

- Absorption of montelukast is rapid following oral administration of the 10 mg FCT, with mean peak plasma concentration (C_{max}) achieved in three to four hours (T_{max}). Mean bioavailability (64%) and C_{max} are not affected by a standard meal in the morning.[21] Mean plasma half-life ranges from 2.7 to 5.5 hours.
- Montelukast and its metabolites are not excreted in the urine, therefore, no dosage adjustment is recommended for patients with renal insufficiency.[22]
- Excretion is almost exclusively via the bile. The elimination of montelukast was slightly prolonged in patients who had mild-to-moderate hepatic insufficiency with clinical evidence of cirrhosis compared with that in healthy subjects. As a result of the large therapeutic index and safety margins for montelukast, no dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency.[22]
- Based on drug interaction studies and available clinical experience, no dosage adjustment for montelukast is recommended upon co-administration with Cytochrome P450 (CYP) enzyme inhibitors or inducers.[22] Thus, no dose adjustment is needed when Singulair is co-administered with a wide variety of commonly used drugs (e.g., oral contraceptives, prednisone, non-steroidal anti-inflammatories, decongestants, etc.). (See **Section 3.4** for further details regarding pharmacology.)

1.4 Review of Clinical Efficacy and Rationale for Inclusion of "Itchy/Watery Eyes" on the Singulair Allergy OTC Label

The efficacy of Rx Singulair for relief of symptoms of AR was demonstrated in the large clinical development program that supported the U.S. approvals for both SAR and PAR.

In the Rx Singulair labeling, efficacy for AR is described on the primary endpoint of Daytime Nasal Symptoms score. During the time when Rx Singulair was being studied for AR, FDA published in 2000 a Draft Guidance for Industry on the topic,[2] which suggested the main measure of effectiveness in AR trials would generally include three or four nasal symptoms depending on the molecule being studied. The

Rx Singulair development program for AR followed this guidance in contrast to other allergy products approved prior to 2000 (including oral antihistamines on the OTC market today), which used a traditional primary endpoint that was a composite of both nasal and non-nasal symptoms.

The Rx Singulair development program also included several secondary endpoints that showed significant efficacy in multiple clinical trials. However, these were not reflected in the label because, at the time of the development program, these endpoints were considered *supportive* of the *primary* efficacy endpoint and an explicit plan (and/or analytic approach) for secondary endpoints to be added to the labeling was not pre-specified. Nevertheless, the eye symptoms associated with AR are well understood by consumers and are described in the current labeling for many products now available OTC for AR.

In the OTC environment, it is important to inform consumers about the key benefits that a medication can provide, as the learned intermediary is typically absent in the decision-making process to use the OTC medication. The requested addition of "itchy/watery eyes" to the OTC Drug Facts label is supported by the efficacy demonstrated via the individual eye symptom scores of "tearing eyes" and "itchy eyes" (using the FDA-recommended 0-3 scale for AR symptoms[2]). As had been shown for the nasal symptoms, montelukast demonstrated significantly greater treatment benefits over placebo on these eye symptoms in 2 of the 3 pivotal Phase III SAR studies, and by pooled data across all 3 trials. (See **Section 4.0** for details.) Importantly, the efficacy of Rx Singulair on these symptoms was similar to that demonstrated on the primary endpoint of nasal symptoms, the basis for approval of Rx Singulair for AR.

Results of these specific eye symptoms efficacy measurements were further supported by significantly greater improvement over placebo when the burden of AR symptoms was assessed in all 4 pivotal AR studies (**Table 1**), by:

- The patient self-administered rhinoconjunctivitis quality of life using a validated questionnaire which provided a broad measure over seven separate domains, including a specific domain for eye symptoms; and
- The patient global evaluation of AR, which provides a simple overall measurement of the patient-perceived benefit of therapy for the clinical manifestation of all symptoms of AR.

In totality, the efficacy profile of montelukast in AR for ocular symptoms is equally as strong as for nasal symptoms, and as such, supports the inclusion of "itchy/watery eyes" symptom relief on the OTC label to enable consumers to make an informed treatment decision.

Table 1 SAR and PAR Pivotal Efficacy Studies

Studies	Number of Patients	Designs	Major Entry Criteria	Efficacy Endpoints[c]
A. In Patients with Seasonal Allergic Rhinitis (SAR)[a]				
Study 162 (Spring 2000) Study 192 (Fall 2000) Study 235 (Spring 2001)	1302 829 1214	Phase III, multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled study in patients 15 years of age and older	• History of SAR during study season • Positive skin test to a seasonal allergen (relevant to the study season) • Predefined level of daytime nasal symptoms during baseline (placebo run-in) period	• Nasal symptom scores (dNSS[d], EoDNSS, nSS, CSS) • Ocular symptom scores (dESS) • Rhinoconjunctivitis quality-of-life • Patient and physician general evaluation of allergic rhinitis (GEoAR)
B. In Patients with Perennial Allergic Rhinitis (PAR)[b]				
Study 265	1992	Phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in patients 15 years of age and older	• History of PAR • Positive skin test to at least two relevant perennial allergen (dust mites, animal dander, and/or mold spores) • Active PAR symptoms at study entry	• Nasal symptom scores (dNSS[e],EoDNSS, nSS, CSS) • Rhinoconjunctivitis quality-of-life • Patient general evaluation of allergic rhinitis (GEoAR)

a Reference: NDA 20-829/S-017; Merck: Montelukast Sodium – Seasonal Allergic Rhinitis. Patients received montelukast (10 mg) or matching placebo once daily in the evening for 2 weeks.

b Reference: NDA 20-829/S-033; Merck: Montelukast Sodium – Perennial Allergic Rhinitis. Patients received montelukast (10 mg) or matching placebo once daily in the evening for 6 weeks.

c dNSS = Daytime nasal symptom score; dESS = Daytime eye symptom score; nSS = Nighttime symptom score; CSS = Composite symptom score (named "daily rhinitis symptom score" in P265); GEoAR = General evaluation of allergic rhinitis; EoDNSS = End-of-day nasal symptoms score

d dNSS defined in SAR studies as the average of individual scores for congestion, rhinorrhea, sneezing, and itching

e dNSS defined in the PAR study as the average of individual scores for congestion, rhinorrhea, and sneezing,

1.5 Review of Safety

This OTC switch application includes the safety information from the following data sources:

- Safety data from the clinical trials in adults which supported the original and supplemental NDAs for SAR, PAR and EIB; (See **Section 5.1** for details.)
- Post-marketing safety adverse event data from: (See **Section 5.3** for details.) Merck's internal adverse event database (Merck Adverse Event Reporting and Review System or MARRS), covering the timeframe of first market introduction in Mexico (July 31, 1997) through March 31, 2013;

- External post-marketing sources covering the timeframe of the U.S. Rx NDA approval, February 20, 1998, through March 31, 2013:
  - AERS (Adverse Event Reporting System);
  - WHO (World Health Organization) VigiBase databases;
  - AAPCC (American Association of Poison Control Centers) database;
  - DAWN (Drug Abuse Warning Network) database.

- Worldwide literature.

Consideration of Clinical Trials Safety Data

The overall Rx Singulair development program, for all dosage forms and all indications, includes more than 100 clinical trials involving more than 20,000 montelukast-treated patients. Across 22 Phase IIb and III trials of the original development program, more than 6,000 patients were treated with montelukast (**Table 2**). None of the serious clinical adverse experiences (SAEs) reported in the Phase IIb/III trials was considered drug-related by the investigators. Within the specific AR development programs, clinical trials have shown montelukast 10 mg to be generally well tolerated in adults. This is consistent with the clinical trial safety data that supported the asthma and EIB indications.

Table 2 Number of Patients Receiving Montelukast in Phase IIb/III Trials

Rx Programs	Studies	No. of Patients Receiving Montelukast
Asthma indication	10 Phase IIb/III clinical studies	2,606
SAR indication	8 Phase IIb/III trials	1,884
PAR indication	2 Phase III trials	1,632
EIB indication	2 Phase III trials	109

Across all indications including AR, the most common adverse reactions (incidence ≥5% and greater than placebo; listed in descending order of frequency) in controlled clinical trials for Singulair were upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis (listed regardless of causality assessment). Further details are provided under **Section 5.1**.

Although somnolence was not expected to be a safety concern with an anti-leukotriene, somnolence-related adverse events (AEs) were examined in detail in the SAR and PAR clinical development program databases because of its association as a safety concern with some OTC AR therapies (e.g., many antihistamines). For montelukast 10 mg and above, the incidence of somnolence and somnolence-related AEs is similar to that seen with placebo.

The short- and long-term safety profile demonstrates that montelukast is generally well tolerated, even at doses substantially above the proposed OTC dose of 10 mg. As noted in the current Rx Singulair labeling, montelukast has been administered in

clinical studies at doses up to 200 mg/day to asthmatic adult patients for 22 weeks; in short-term clinical studies, montelukast has been administered at doses up to 900 mg/day (300 mg TID) for approximately 1 week without clinically important adverse experiences.

Post-Marketing Safety Considerations

Post-Marketing Safety Data Review – Merck Database

As part of the ongoing safety surveillance of montelukast, Merck regularly reviews post-marketing safety data in order to further characterize the safety profile. Singulair has more than 16 years of use in the market for both adults and children, in more than 100 countries.

A review of post-marketing data received by Merck for montelukast (all doses, age groups and indications) from healthcare providers (HCPs), regulatory agencies, and consumers from market introduction to March 31, 2013 was performed. A total of 46,527 Individual Case Safety Reports (ICSRs) were identified. The majority (71%) of these ICSRs were non-serious.

The Rx Singulair label lists six *Warnings and Precautions*, five of which will be discussed in this briefing document. The first four of these warnings apply specifically to the asthma patient population (acute asthma, concomitant inhaled corticosteroid use for asthma, aspirin-sensitive asthma, and systemic eosinophilia in patients with asthma), and while MCC is only pursuing OTC status for the AR indication, these warnings will be covered briefly due to the high co-morbidity of allergy and asthma. The fifth warning, phenylketonuria, will not be discussed since this warning is specific to the chewable-tablet formulation. The sixth warning on the Rx Singulair label pertains to neuropsychiatric events, and is applicable for both allergies and asthma. This warning will be the focus of the post-marketing review within this briefing document.

Approximately 25% of all the post-marketing ICSRs received for montelukast describe one or more events in the Psychiatric System Organ Class (SOC). Similar to all ICSRs received for montelukast, the majority (73%) of ICSRs with one or more events in the Psychiatric SOC were non-serious. While a mechanism of action is not understood, these events are included in the Rx Singulair labeling and have been proposed for the OTC Drug Facts label as well.

The overall benefit/risk profile of Rx Singulair is favorable. Consistent with the Rx Singulair labeling, the OTC product has proposed the Drug Facts label alerts patients to these events as well. The clinical terms describing these events are provided in the Rx Patient Package Insert and will also be represented in a leaflet in the OTC product package.

Post-Marketing Safety Data Review – Public Databases

Safety data were obtained and analyzed from FDA AERS, WHO VigiBase (ex-U.S.), AAPCC, and DAWN databases. The review of these external post-marketing safety databases, as outlined in **Section 5.0** of this briefing document, demonstrated that these data were consistent with what has been identified in clinical trials and in the Merck post-marketing safety database.

PubMed was queried for English language Singulair/montelukast literature and no new safety concerns were identified.

1.6 Topics Relevant to this Rx-to-OTC Switch Application

Potential Off-Label Use to Treat Asthma

Rx Singulair is indicated for AR and asthma. Due to their prior experience with the Rx product, some individuals may potentially use the OTC product off-label to help manage their asthma. This concern about potential off-label use of an OTC product is not unique for Singulair Allergy. As mentioned earlier, many OTC products such as Proton Pump Inhibitors to treat frequent heartburn, NSAIDs to reduce fever and relieve minor aches and pains, and topical antifungals to treat athlete's foot, jock itch, and ringworm remain Rx for higher doses and/or for other indications, such as peptic ulcer disease and erosive esophagitis, rheumatoid arthritis and osteoarthritis, and *tinea versicolor*, respectively. OTC Drug Facts labels inform consumers when to see a doctor for a potentially more serious condition to assure safe use in the nonprescription setting

Singulair Allergy is very clearly labeled for the treatment of AR and not for the treatment of asthma. Importantly, the OTC development program (in **Section 8.0**) has demonstrated that this key communication message is well understood by consumers. The proposed OTC labeling is detailed in **Section 7.0**.

The OTC label was developed to minimize any potential incremental risk of people with asthma using this product to treat their asthma without the benefit of an HCP. The following safeguards have been incorporated into the Singulair Allergy label to mitigate the theoretical risk of off-label use for asthma in the OTC environment:

- The proposed product name is "Singulair Allergy" which is prominently displayed on the front and side panels;
- The statement "For indoor and outdoor allergies" appears on front panel of the carton;
- The statement "for allergies" appears prominently on the front panel of the carton;
- The statement "**THIS PRODUCT IS ONLY FOR ALLERGIES. DO NOT USE TO TREAT ASTHMA**" is featured above the Drug Facts label in a bright yellow box with bolded, capitalized letters;

- A warning on the Drug Facts label states, "Do not use to treat asthma. Asthma can be a life-threatening condition, and you should follow your doctor's directions."
- Consumers currently taking asthma medicines are warned to "not stop taking them."

This topic was thoroughly addressed as a key component of the OTC development plan. The Singulair OTC Label Interpretation and Decisions consumer study (SOLID) demonstrated that people with asthma appropriately self-selected not to use Singulair Allergy to treat their asthma. The study also demonstrated that key warnings and directions on the OTC label were well understood. Thus, the concern regarding the four asthma-related warnings currently on the Rx Singulair label (acute asthma, concomitant inhaled corticosteroid use for asthma, aspirin-sensitive asthma, and systemic eosinophilia in patients with asthma) is very low and is not relevant for this OTC Drug Facts label. Details of this study can be found in **Section 8.3**.

Behavior and Mood-Related Changes

Behavior and mood-related changes have been reported with Rx Singulair and are reflected in the Rx Singulair labeling. MCC has carefully developed consumer language to clearly communicate to OTC consumers that they should "stop use and ask a doctor" if they experience unexpected behavior and mood-related changes.

Specifically, the following warnings are included on the OTC Drug Facts label:

Stop use and ask a doctor if

- You experience unexpected changes in behavior, thoughts or mood
- You experience unexpected changes or problems when you sleep

These warnings were tested among both adults and teens in our development program:

- Label Comprehension Warnings Study (13007) among adults ≥18 years old, with AR;
- Teen Self-Selection and Warning Interpretation Study (13023) among teens, 15-17 years old, with AR.

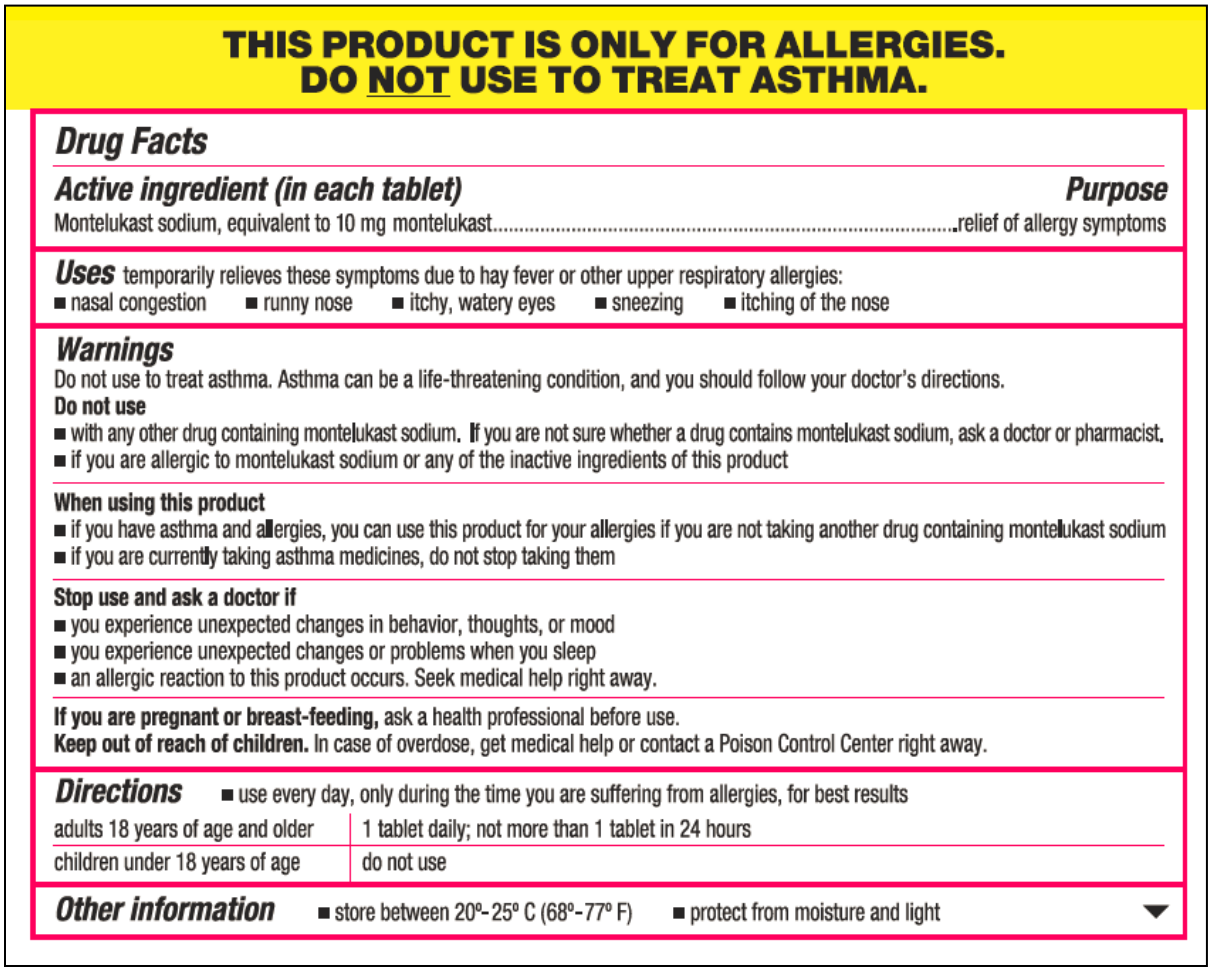
Study details can be found in **Sections 8.4** and **8.5**, respectively.

1.7 Proposed Singulair Allergy Labeling

The proposed OTC labeling for Singulair Allergy was based on current OTC antihistamine labeling (given the similarity in target population and symptoms), the Rx Singulair labeling, consumer research findings, and from interaction with FDA. As with any potential switch, the Singulair Allergy OTC Drug Facts label was

developed to incorporate the most pertinent information needed for consumers to safely use the product without the benefit of an HCP, in consumer-friendly language and in line with FDA's standard OTC labeling requirements. The OTC allergy category labeling for first generation antihistamines is codified in the OTC final monograph 21 CFR Part 341 and has been on marketed OTC allergy products for decades. Similarly, the Singulair Allergy label was aligned as appropriate with the labeling for existing products to minimize consumer confusion.

Figure 1 Singulair Allergy Drug Facts label Tested in OTC Development Program



THIS PRODUCT IS ONLY FOR ALLERGIES.
DO NOT USE TO TREAT ASTHMA.

Drug Facts

Active ingredient (in each tablet) ***Purpose***

Montelukast sodium, equivalent to 10 mg montelukast.....relief of allergy symptoms

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
- nasal congestion
- runny nose
- itchy, watery eyes
- sneezing
- itching of the nose

Warnings

Do not use to treat asthma. Asthma can be a life-threatening condition, and you should follow your doctor's directions.

Do not use
- with any other drug containing montelukast sodium. If you are not sure whether a drug contains montelukast sodium, ask a doctor or pharmacist.
- if you are allergic to montelukast sodium or any of the inactive ingredients of this product

When using this product
- if you have asthma and allergies, you can use this product for your allergies if you are not taking another drug containing montelukast sodium
- if you are currently taking asthma medicines, do not stop taking them

Stop use and ask a doctor if
- you experience unexpected changes in behavior, thoughts, or mood
- you experience unexpected changes or problems when you sleep
- an allergic reaction to this product occurs. Seek medical help right away.

If you are pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions - use every day, only during the time you are suffering from allergies, for best results

adults 18 years of age and older	1 tablet daily; not more than 1 tablet in 24 hours
children under 18 years of age	do not use

Other information - store between 20°-25° C (68°-77° F) - protect from moisture and light

In addition to the Drug Facts label, MCC has proposed a CIL that will provide more details about the warnings related to unexpected changes in behavior, thoughts, mood or sleep. This CIL is based on language from the Rx patient package insert that is currently provided to users of Rx Singulair today.

1.8 Singulair Allergy OTC Development Program

The development program demonstrated the key program goals:

- People with asthma understood the key messages on the Drug Facts label: not to use Singulair Allergy to treat their asthma and to not stop taking their asthma medications;
- The behavior-related warnings were well understood among adults and teens;
- Teens understood Singulair Allergy is only to be used by adults 18 years of age and older.

Three consumer self-selection and label comprehension studies were conducted (**Table 3**)**.** The summary results are as follows:

- The SOLID study, a combined targeted self-selection and label comprehension study, addressed the concern about the potential for off-label use of Singulair Allergy by subjects with asthma, with and without AR. The study enrolled people with asthma, with and without AR, and the results of this study demonstrated that they can correctly self-select to use or not to use Singulair Allergy based on the label and their own health history. They understood the key safety messages that Singulair Allergy is not to be used to treat asthma and to not stop using their asthma medications when using Singulair Allergy.
- Two additional targeted consumer studies were conducted to specifically evaluate self-selection and understanding of mood-related warnings. The first was a label comprehension study among a general population of adults 18 years of age and older with AR, and the second was a self-selection and label interpretation study among a general population of adolescents with AR, ages 15-17. Both studies showed that adults and adolescents understood the age directive and the warnings.

FDA did not request an Actual Use Study to support this partial OTC switch application because the AR category is well established with many other OTC medications and Singulair Allergy has a similar dosing form and regimen to these already approved products.

Table 3 Consumer Studies – Summary of Results

Study/Objective	Results
SOLID: To establish that people with asthma (both with and without prior experience with Rx Singulair) understand that Singulair Allergy should not be used to treat asthma.	**% Correct Self-Selection** • With Prior Rx Singulair Experience: 91.7% (88.4% LB) • Without Prior Rx Singulair Experience: 96.3% (93.7% LB) • Subjects who have Low Literacy Skills: 90.8% (85.3% LB) **Label Comprehension of Primary Medical Risk Warnings** *"Do not use to treat asthma"* • With Prior Rx Singulair Experience: 91.7% (88.4% LB) • Without Prior Rx Singulair Experience: 92.3% (88.9% LB) • Subjects who have Low Literacy Skills: 79.1% (72.1 % LB) *"If you are currently taking asthma medications, do not stop taking them"* • With Prior Rx Singulair Experience: 94.0% (91.2% LB) • Without Prior Rx Singulair Experience: 96.0% (93.4% LB) • Subjects who have Low Literacy Skills: 87.7% (81.7 % LB) *"Children under 18 years of age, do not use"* • With Prior Rx Singulair Experience: 95.8% (93.3% LB) • Without Prior Rx Singulair Experience: 96.8% (94.4% LB) • Subjects who have Low Literacy Skills: 91.4% (86.0% LB)
Label Comprehension Warnings Study: To demonstrate that the behavior and mood-related warnings (BRAE) are well understood by adults with AR.	**Label BRAE Warnings: % Correct Comprehension:** *"Stop use and ask a doctor if you experience unexpected changes in behavior, thoughts or mood"* • 97.5% (95.3% LB) *"Stop use and ask a doctor if you experience unexpected changes or problems when you sleep":* • 97.0% (94.4% LB)
Self-Selection and Warning Interpretation among Adolescents: To assess that 15-17 year olds understand that Singulair Allergy is intended only for adults and also to understand that these teens understand the behavior and mood-related warnings (BRAE).	**% Correct Self-Selection:** 84.3% (80.0% LB) **Safe-Intended Action:** 96.6% (94.1% LB) **BRAE Warnings:** % Correct Interpretation**:** 95.1-95.7% (92.3-93.0% LB)

BRAE = Behavior Related Adverse Event
LB = Lower Bound of the 95% Confidence Interval (CI)

1.9 Benefit and Risk Considerations

Benefits for the OTC Environment

Singulair Allergy would offer an important alternative to available OTC therapies for the treatment of AR in adults 18 years of age and older. Singulair Allergy has a unique mechanism of action compared to other OTC drugs approved for the treatment of AR and, therefore, will offer consumers a new treatment option. Singulair Allergy would provide consumers with non-sedating, comprehensive symptom relief with convenient once-daily dosing. It would offer distinct benefits to consumers, such as the relief of nasal congestion in a single ingredient tablet, with few, if any, of the limitations present in the category today. Singulair Allergy has a favorable tolerability profile, an absence of clinically-significant interaction with other medications or food, and no limitations based on co-morbidities. In addition, there are no contraindications or need for dose adjustment in the elderly or in adults with hepatic or renal impairment. In summary, the OTC approval of Singulair Allergy would afford millions of people with allergies an important new choice to self-manage their AR.

Incremental Risks in the OTC Environment

Incremental risk describes the potential for unintended consequences resulting solely from OTC availability of a previously prescription-only product and the lack of direct involvement with an HCP. When considering whether a product is an appropriate OTC candidate, it is important to consider the degree of incremental risk, above the current level of risk that exists in the prescription environment. There are two important topics related to incremental risk considered to be relevant to this switch:

1. The potential for patients with asthma to use this product off-label in an OTC setting to treat their asthma; and
2. Communication of behavior and mood-related warnings to consumers.

The OTC labeling was developed to address these topics and the relevant warnings were well understood by over 90% of subjects.

In addition to the warnings on the proposed Drug Facts label, MCC also proposes a CIL to provide additional information about unexpected changes in behavior, thoughts, mood, or sleep using language identical with the Rx patient package insert as shown in **Appendix 1**.

Therefore the benefits of broader access to Singulair Allergy for people with AR outweigh the potential for incremental risks that have been demonstrated to be appropriately managed with clear and well-understood labeling.

1.10 Overall Rationale Supporting Singulair Allergy

Expanding access to safe and convenient OTC options with different mechanisms of action can help the millions of consumers who self-manage their AR.

The clinical development program and the experience gained over the last 16 years have demonstrated that Singulair Allergy will provide an efficacious and well-tolerated new therapy in the OTC environment with the benefits of a non-sedating, once-daily single-ingredient tablet available to treat all major allergy symptoms, including nasal congestion. Montelukast has a mechanism of action different from any other agent approved OTC for the treatment of AR.

The incremental risks associated with OTC availability of Singulair Allergy have been evaluated using a comprehensive review of clinical studies, post-marketing events, and literature searches. MCC has addressed the potential for incremental risk through the development of OTC product labeling which has been validated through label comprehension and self-selection studies, demonstrating that the proposed Drug Facts label, which includes information about indication, warnings and appropriate age for use, was well-understood by consumers. Thus, the risks associated with Singulair Allergy in the OTC environment are minimal and comparable to those that currently exist with use of the Rx product.

The data demonstrate that the benefits of broader access to OTC Singulair Allergy, with its new mechanism of action for the OTC environment, outweigh the risks. For all these reasons, Singulair Allergy is well-suited as an additional option for people with AR who choose to self-manage their allergies with OTC medicines.

2.0 AR: PATHOPHYSIOLOGY, QUALITY OF LIFE AND CURRENT SELF-MANAGEMENT TREATMENT OPTIONS

Nearly 75 million people in the U.S. are affected by AR[4,5] , a condition characterized by symptoms of nasal congestion, rhinorrhea, sneezing, and nasal pruritus (itchy nose) as well as additional non-nasal symptoms including eye itching, and eye tearing.[6] When the nasal mucosa of a sensitized patient is exposed to an airborne allergen, airway inflammatory cells, including mast cells and eosinophils, are activated.[23] These cells undergo degranulation to release histamine, and rapidly synthesize a mixture of inflammatory mediators including CysLTs, prostaglandin D2, and kinins, which attract additional inflammatory cells into the nasal submucosa.[24] Currently, only the CysLTs have been identified as being important in the inflammatory process associated with AR. Increased CysLT concentrations are measurable in nasal secretions of patients with AR and cause upper airway edema, mucus secretion, and eosinophil migration. These reactions correspond to airway inflammation in AR and, ultimately, result in the classic AR symptoms.[23]

2.1 Current Self-Management Treatment Options

Few people with AR seek care from a physician and most patients with allergies turn to OTC medications for self-treatment.[13] According to a 2013 survey by the Consumer Healthcare Products Association, 90% of people with AR self-treat their symptoms regularly or occasionally.[14] In addition, nearly 60% only use OTC medicines or herbal/homeopathic products for their symptoms.[12]

Currently approved OTC agents specifically indicated for the treatment of AR symptoms are summarized below, highlighting their benefits and limitations:

- **Oral H_1-antihistamines**: First-generation antihistamines are effective at relieving most symptoms of AR but high penetration into the central nervous system results in well-known sedative effects.[15] When using these products, users must use caution when driving or operating machinery and should avoid alcoholic beverages. First-generation antihistamines are also non-selective and have anticholinergic effects that commonly result in dry mouth and, rarely, in serious cardiac dysrhythmias.[15]

Second-generation antihistamines have an improved adverse event profile versus the first generation but their use may be limited by drug-drug and/or drug-food interactions.[1,46] Antihistamines do not relieve nasal congestion, which is reported to be the most common and bothersome symptom of AR.[10,13]

- **Combination Oral Antihistamines/Decongestants:** Pseudoephedrine (PSE) and phenylephrine (PE) are nasal decongestants frequently combined with antihistamines.

PSE is an effective nasal decongestant. Adverse events include nervousness, agitation, palpitations, and insomnia. As a result, the Drug Facts label for nonprescription products containing PSE cautions users to consult a doctor before use if they have liver or kidney disease, heart disease, high blood pressure, thyroid disease, diabetes or trouble urinating due to an enlarged prostate gland.[16,17] PSE may be obtained only in small quantities from the pharmacist after the presentation of valid identification.

PE is another alpha-agonist decongestant frequently combined with antihistamines. It has a similar adverse event profile to PSE and has a short half-life, so its effect does not last and dosing must be repeated every 4 hours.[18]

- **Intranasal Cromolyn**: This ingredient acts by stabilizing degranulation of mast cells leading to histamine release and has modest efficacy, and can be dosed 4-6 times daily. Also, it is recommended to initiate therapy one week in advance of anticipated contact with seasonal allergens.[19]

- **Intranasal Corticosteroids:** The most recently approved OTC AR medication is triamcinolone acetonide. Intranasal corticosteroids are an effective treatment for reducing inflammation of the nasal mucosa, but it may take up to one week of daily use to feel the most symptom relief. Nasal sprays are not the most preferred dosage form for the treatment of allergies and may be rejected by some people.[20]

All of these currently available OTC treatments exert their effect through a variety of actions but none act directly on CysLT receptors, the targeted mechanism of action of Singulair Allergy. Therefore, Singulair Allergy would be the only single-ingredient tablet to offer many of the same treatment benefits as existing OTC products for AR, but also offer distinct benefits to consumers, such as the relief of nasal congestion in a single-ingredient tablet, with less of the limitations present in the category today. It can be used without sedation, or without concern for drug or food interactions or anticholinergic effects. People with liver or kidney disease, cardiovascular issues, diabetes, hypertension, glaucoma, thyroid disease, or prostate hyperplasia who, therefore, are limited in what they can use for AR, can safely use Singulair.

2.2 AR Impact on Quality of Life

Although not life threatening, AR is lifestyle-limiting and has a well-documented impact on health-related and overall quality of life (QoL) measures. A survey has shown that 40% of people with allergies report that their allergies have a moderate to significant impact on their daily lives.[9] Studies have shown that AR symptoms cause sleep disturbances in as many as 76% of patients, and negatively impact cognitive processing/memory and decision making.[1] In the U.S., AR accounts for a greater loss of productivity than any other illness, with an estimated 10 million missed workdays each year.[11] In 2005, overall direct and indirect costs attributable to AR totaled $11.2 billion, nearly doubling the dollar spent in 2000.[25,26]

2.3 A New OTC Option for People with Allergies

Though all OTC AR medications have been proven effective, each medicine does not optimally suit everyone due to individual responses to medication.[1] Singulair Allergy 10 mg is well suited for AR treatment in an OTC environment as it provides non-sedating, 24-hour symptomatic relief of a broad range of nasal and non-nasal (specifically, ocular) symptoms in a convenient single-ingredient tablet. Montelukast, a leukotriene blocker, provides a favorable benefit-risk profile for the treatment of AR in an environment where a majority of people with allergies self-manage with current OTC antihistamines. Montelukast has shown prolonged, demonstrable, and reproducible benefit with once-daily dosing, making it well suited as an OTC medication for AR. Montelukast has demonstrated excellent tolerability, has no clinically important drug-drug interactions, possesses a safety profile similar to that of placebo in clinical trials, can be administered safely to subjects with co-morbidities (such as diabetes mellitus, cardiovascular diseases, glaucoma), provides treatment benefits consistent without regard to age, gender, ethnicity or timing of administration, and showed persistent beneficial effects across the entire dosing interval and treatment course.

Because AR is not usually associated with permanent or serious sequelae, patient assessment of symptomatic relief is the main clinical outcome. Therefore, any product that meets all these criteria will be an important option for consumers. Singulair Allergy has been shown to meet all of these criteria.

3.0 APPROVAL HISTORY, MECHANISM OF ACTION AND PHARMACOLOGY

3.1 Regulatory History

Rx Singulair (montelukast sodium) was first approved in Mexico in 1997. The U.S. regulatory approval history for Rx Singulair 10 mg FCT is summarized by the following major milestones:

1998: First US FDA approval; indicated for prophylaxis and chronic treatment of asthma in patients 15 years and older.

2002: Additional US indication approved for the relief of the symptoms of SAR in patients 15 years and older.

2005: US indication modified to include for the relief of symptoms of PAR in patients 15 years and older.

2007: Additional US Indication approved to include acute prevention of EIB in patients 15 years and older.

3.2 Formulation, Dosage and Administration

Singulair Allergy 10 mg film-coated tablet is the same dose and formulation approved for Rx use to treat symptoms of AR in adults. Each 10 mg beige, rounded square, film coated tablet contains 10.4 mg montelukast sodium, which is equivalent to 10.0 mg of montelukast.

Dosage Form: 10 mg film-coated tablet

Route of Administration: Oral

Dosage Regimen: Adults 18 years of age and older: take 1 tablet daily; no more than 1 tablet in a 24-hour period. Children under 18 years of age: do not use.

3.3 Mechanism of Action

Montelukast is an orally active leukotriene receptor antagonist which binds with high affinity and selectivity to the $CysLT_1$ receptor of the human airway in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic. CysLTs are not currently known to have any major role in normal physiologic function. Rather, they correlate with the pathophysiology of conditions associated with the inflammatory process. In AR, CysLTs are released from inflammatory cells when they enter an activated state in response to airborne allergen stimulation of the nasal mucosa, during both early- and late-phase allergic reactions. CysLTs cause airway edema, mucus secretion and eosinophil migration; reactions which correspond to the major findings of airway inflammation in AR.[23] By selectively blocking the leukotriene receptor sites, montelukast inhibits actions of the CysLTs involved in the inflammatory process.

3.4 Pharmacology

The pharmacokinetic profile of montelukast is similar in males and females, and is similar with morning or evening dosing. In adult subjects in the fasted state, montelukast 10 mg FCT is rapidly absorbed following oral administration with a mean peak plasma concentration (C_{max}) achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability (64%) and C_{max} are not affected by a standard meal. Efficacy was demonstrated across different clinical studies of AR in which montelukast was administered either once daily in the evening or once daily in the morning. In all clinical studies of AR, patients took montelukast without regard to the time of food ingestion.

Montelukast is extensively metabolized. In studies with the 10-mg FCT, plasma concentrations of metabolites of montelukast are undetectable at steady state in adult patients. *In vitro* studies have shown that montelukast is a substrate of CYP 2C8, 2C9, and 3A4. In clinical drug interaction studies, montelukast at a dose of 10 mg once daily, dosed to pharmacokinetic steady state, did not cause clinically important effects on the pharmacokinetics of theophylline (predominantly a cytochrome P450 (CYP450) 1A2 substrate), prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine (a substrate of CYP3A4), digoxin, and warfarin (primarily a substrate of CYP2C9, 3A4 and 1A2). Although additional specific interaction studies were not performed, in clinical efficacy and safety studies Rx Singulair was used concomitantly with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Although montelukast is a potent inhibitor of CYP2C8 in vitro, data from a clinical drug-drug interaction study support that montelukast does not inhibit CYP2C8 *in vivo*, and therefore, is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide). CYP450 enzyme inducers (e.g. phenobarbital) have been shown to decrease the area under the curve (AUC) for plasma concentration of montelukast by approximately 40%. A clinical drug-drug interaction study with gemfibrozil (an inhibitor of both CYP2C8 and 2C9) demonstrated an increase in the systemic exposure of montelukast by 4.4-fold. However, based on available clinical experience, no dosage adjustment of montelukast is required upon co-administration with such cytochrome modifiers.

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile. Patients who had mild-to-moderate hepatic insufficiency with clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean plasma levels of montelukast following a single 10-mg dose. Based on

available clinical experience, no dosage adjustment of montelukast is required in patients with mild-to-moderate hepatic insufficiency.

Based on several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10 mg montelukast, there is little accumulation of the parent drug in plasma (14%).

4.0 REVIEW OF CLINICAL EFFICACY

MCC has proposed a partial Rx-to-OTC switch of Rx Singulair for the treatment of AR in adults 18 years of age and older. The efficacy of Rx Singulair for relief of symptoms of AR was well demonstrated in the large clinical development program that supported the U.S. approvals for both SAR and PAR, consisting of 10 clinical studies. Within these studies, data from the 4 double-blind placebo-controlled pivotal studies (3 in SAR and 1 in PAR)[41,42] make up the core efficacy that supported approval of the AR indication (**Table 4**).

As acknowledged in the FDA Draft Guidance,[2] variability among studies is not unexpected in development programs of medications for AR, due in part to the subjective nature of the assessments and spontaneous variability in the disease. Thus, a negative study in a development program does not necessarily indicate that the overall efficacy of the drug under study is not clinically meaningful. In the clinical development program of Rx Singulair for AR, one of the SAR studies did not show a statistically significant benefit on the primary endpoint of Daytime Nasal Symptoms score. Additional analyses suggest that the lower level of efficacy in this study (Study 192), compared with the other 2 SAR studies (Studies 162 and 235), may be attributed to the lower levels of pollen counts that were noted during the conduct of Study 192.[27] Nevertheless, the overall level of efficacy of Rx Singulair, as demonstrated in 2 of 3 Pivotal SAR studies and 1 Pivotal PAR study, was deemed by FDA to be statistically significant and clinically relevant, supporting the approval (and subsequent wide use) of Rx Singulair for relief of symptoms of AR.

No new efficacy trials were conducted for this Rx-to-OTC switch.

MCC has requested to include ocular symptoms relief (specifically “itchy/watery eyes”) as part of the OTC label indication though they are not part of the Rx label to give consumers the most appropriate information about Singulair Allergy efficacy, as montelukast has been shown to improve these symptoms during its development program. AR patients generally suffer from a constellation of symptoms that are not only limited to the nose. Although sneezing, nasal itching, runny nose, and nasal congestion are important symptoms of AR, others including itchy/watery eyes, have been identified to be equally as bothersome for AR patients.[6,7]

To support the inclusion of “itchy/watery eyes” in the OTC label for Singulair Allergy, pooled efficacy data for ocular symptoms relief from the AR clinical development program are provided within this section, as well as a comparison of the magnitude of the effect between nasal symptoms and eye symptoms. To further support the clinical relevance of the efficacy data, pooled analyses of the overall burden of AR, as assessed by a patient self-rated quality of life questionnaire and global evaluation of their AR condition, are included.

Pooled efficacy is presented here because the individual studies were neither powered nor designed to demonstrate statistical significance for the secondary

endpoints. However, individual study data for all pooled analyses has been provided in **Appendices 2** and **3**.

Table 4 SAR and PAR Pivotal Efficacy Studies

Studies	Number of Patients	Designs	Major Entry Criteria	Efficacy Endpoints[c]
A. In Patients with Seasonal Allergic Rhinitis (SAR)[a]				
Study 162 (Spring 2000) Study 192 (Fall 2000) Study 235 (Spring 2001)	1302 829 1214	Phase III, multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled study in patients 15 years of age and older	• History of SAR during study season • Positive skin test to a seasonal allergen (relevant to the study season) • Predefined level of daytime nasal symptoms during baseline (placebo run-in) period	• Nasal symptom scores (dNSS[d], EoDNSS, nSS, CSS) • Ocular symptom scores (dESS) • Rhinoconjunctivitis quality-of-life • Patient and physician general evaluation of allergic rhinitis (GEoAR)
B. In Patients with Perennial Allergic Rhinitis (PAR)[b]				
Study 265	1992	Phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in patients 15 years of age and older	• History of PAR • Positive skin test to at least two relevant perennial allergen (dust mites, animal dander, and/or mold spores) • Active PAR symptoms at study entry	• Nasal symptom scores (dNSS[e],EoDNSS, nSS, CSS) • Rhinoconjunctivitis quality-of-life • Patient general evaluation of allergic rhinitis (GEoAR)

a. Reference: NDA 20-829/S-017; Merck: Montelukast Sodium – Seasonal Allergic Rhinitis. Patients received montelukast (10 mg) or matching placebo once daily in the evening for 2 weeks.
b. Reference: NDA 20-829/S-033; Merck: Montelukast Sodium – Perennial Allergic Rhinitis. Patients received montelukast (10 mg) or matching placebo once daily in the evening for 6 weeks.
c. dNSS = Daytime nasal symptom score; dESS = Daytime eye symptom score; nSS = Nighttime symptom score; CSS = Composite symptom score (named "daily rhinitis symptom score" in P265); GEoAR = General evaluation of allergic rhinitis; EoDNSS = End-of-day nasal symptoms score
d. dNSS defined in SAR studies as the average of individual scores for congestion, rhinorrhea, sneezing, and itching
e. dNSS defined in the PAR study as the average of individual scores for congestion, rhinorrhea, and sneezing

4.1 Rationale for Inclusion of "Itchy/Watery Eyes" on the Singulair Allergy OTC Label

In the Rx Singulair labeling, the approved efficacy for AR is based on the primary endpoint of Daytime Nasal Symptoms score which includes the symptoms of nasal congestion, rhinorrhea, nasal itching and sneezing, and supported by significant improvement in several secondary endpoints.

During the period when Rx Singulair was being studied for AR, FDA published in 2000 a Draft Guidance for Industry on the topic, "Allergic Rhinitis: Clinical Development Programs for Drug Products," which suggested the main measure of effectiveness in AR trials would generally include three or four nasal symptoms (rhinorrhea, nasal congestion, nasal itching, and sneezing) depending on the molecule being studied. The Rx Singulair development program for AR followed this guidance. This is in contrast to other allergy products approved prior to 2000 (including oral antihistamines on the OTC market today), which used a traditional primary endpoint that was a composite of both nasal and non-nasal symptoms.

The Rx Singulair development program also included several secondary endpoints that showed significant efficacy in multiple clinical trials. These secondary endpoints are not reflected in the label because, at the time of the development program, they were considered supportive of the primary efficacy endpoint of the Daytime Nasal Symptoms score. Stated differently, the development program in the early 2000's did not pre-specify an explicit plan (and/or analytic approach) for secondary endpoints to be added to the labeling. Daytime Eye Symptoms scores were part of secondary endpoints in the SAR development program for Rx Singulair.

In the OTC environment, it is important to inform consumers about all the documented benefits that a medication can provide, as the learned intermediary is typically absent in the decision-making process to use the OTC medication. To support inclusion of "itchy/watery eyes" in the OTC label for Singulair Allergy, ocular data from the AR clinical development program are summarized below. Furthermore, the eye symptoms associated with AR are well understood by consumers and are described in the current labeling for many products now available OTC.

4.2 Eye Symptoms Scores and Eye Symptoms Domain of the Rhinoconjunctivitis Quality of Life Questionnaire

This section provides pooled efficacy data from the original Rx supplemental NDAs for AR, including 4 double-blind, placebo-controlled, Phase III studies: 3 in SAR and 1 in PAR (**Table 4**). The individual study data are included in **Appendices 2** and **3.**

Overall Daytime Eye Symptoms Scores and individual symptoms scores (including "itchy eyes" and "tearing eyes") were assessed in the 3 pivotal SAR studies, and demonstrated significant improvement versus placebo in the pooled analyses (**Table 5**). Moreover, the efficacy of Rx Singulair on eye symptoms was similar to that

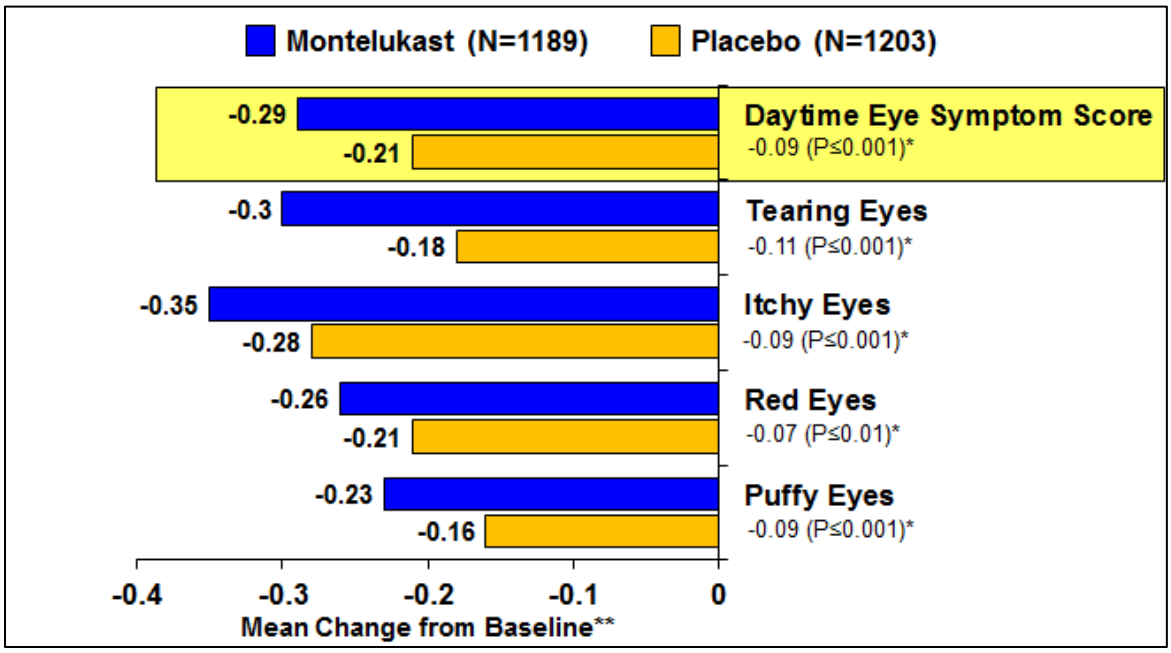
demonstrated on the primary endpoint of nasal symptoms, the basis for approval of Rx Singulair for AR, as demonstrated by the comparable magnitude of the effect on the overall Daytime Nasal and Eye Symptoms scores, respectively (**Table 6**). The individual symptoms composing the overall daytime nasal and ocular scores also showed similar magnitudes of effect (**Table 7**) in the pivotal SAR studies (no comparison was made from the pivotal PAR study since Daytime Eye Symptoms Score was not measured in that study).

To further support the clinical relevancy of the efficacy data, and because symptoms of AR can be extremely bothersome for patients and affect quality of life, patients self-assessed their rhinoconjunctivitis quality of life (RQoL) using a validated questionnaire.[28] The questionnaire contained 28 items to provide a broad measure of the burden of AR over 7 separate domains. Within the specific Eye Symptoms domain in all 4 pivotal AR studies, montelukast demonstrated significantly greater treatment benefit over placebo in 3 of the 4 studies (**Table 8**). These results are consistent and reflect the efficacy improvements observed in the assessments of the AR-associated nasal and ocular symptoms.

Overall, the preponderance of the available evidence supports the requested addition of “itchy/watery eyes” to the OTC Drug Facts label because:

1. The Daytime Eye Symptoms score demonstrated positive efficacy in 2 of the 3 pivotal SAR studies as well as the individual symptoms scores, specifically, “tearing eyes” and “itchy eyes” (**Appendix 2**);
2. The pooled efficacy analysis of the Daytime Eye Symptoms score of the 3 pivotal SAR studies demonstrated positive efficacy, as well as for the individual symptoms scores, specifically, “tearing eyes” and “itchy eyes” (**Table 5**);
3. The effect sizes of the efficacy in the pooled analyses of the 3 pivotal SAR studies are comparable for both Daytime Eye Symptoms score and Daytime Nasal Symptom score (the basis for approval of Rx Singulair for AR) (**Table 6**), as well as for the individual symptoms that composed these scores (**Table 7**).
4. The improvement in the burden of these symptoms, as assessed by the patient quality-of-life questionnaire, specifically, the eye symptoms domain from the pooled pivotal SAR studies as well as the pivotal PAR study, was significant for montelukast over placebo (**Table 8**).

Table 5 Daytime Eye Symptoms Score and Individual Eye Symptoms: Pooled Pivotal SAR Studies



*LS Mean Difference (P-Value)
**Evaluated on a scale from 0 (absent symptoms) – 3 (severe symptoms)

Table 6 Pooled SAR Studies: Comparison of Overall Daytime Nasal Symptoms Score and Overall Daytime Eye Symptoms Score

	N†		Mean Baseline (Score)		Change from Baseline (Score) (Mean ± SE)		Difference in LS Means (95% CI)	p-Value
	M	PBO	M	PBO	M	PBO	Montelukast Minus Placebo	
Overall Daytime Nasal	1189	1203	2.11	2.12	-0.38±0.02	-0.29±0.02	-0.10 (-0.14,-0.05)	p≤0.001
Overall Daytime Eye			1.45	1.48	-0.29±0.02	-0.21±0.02	-0.09 (-0.13,-0.05)	

†N = Number of patients included in the modified intention-to-treat (mITT) analysis
M: montelukast; PBO: Placebo; LS Mean: Least-Squares Mean; CI: Confidence Interval; SE: Standard Error
References: NDA 20-829/S-017 (Merck: Montelukast Sodium – Seasonal Allergic Rhinitis); Clinical and Statistical Documentation; Section D, Table D-4, Table D-11.

Table 7 Pooled SAR Studies: Comparison of Individual Daytime Nasal Symptoms Scores and Individual Daytime Eye Symptoms Scores

	Symptoms	N†		Mean Baseline (Score)		Change from Baseline (Score) (Mean ± SE)		Difference in LS Means (95% CI)	p-Value
		M	PBO	M	PBO	M	PBO	Montelukast Minus Placebo	
Indiv. Daytime Nasal	Congestion	1189	1203	2.35	2.37	-0.38±0.02	-0.29±0.02	-0.10 (-0.14,-0.05)	p≤0.001
	Rhinorrhea			2.12	2.13	-0.41±0.02	-0.32±0.02	-0.10 (-0.15,-0.05)	
	Itching			2.02	2.04	-0.38±0.02	-0.32±0.02	-0.07 (-0.12,-0.02)	p≤0.01
	Sneezing			1.94	1.92	-0.37±0.02	-0.24±0.02	-0.12 (-0.17,-0.07)	
Indiv. Daytime Eye	Tearing Eyes	1189	1203	1.46	1.44	-0.30±0.02	-0.18±0.02	-0.11 (-0.13,-0.06)	p≤0.001
	Itchy Eyes			1.87	1.91	-0.35±0.02	-0.28±0.02	-0.09 (-0.14,-0.04)	
	Red Eyes	1188		1.32	1.38	-0.26±0.02	-0.21±0.02	-0.07 (-0.11,-0.02)	p≤0.01
	Puffy Eyes			1.16	1.21	-0.23±0.02	-0.16±0.02	-0.09 (-0.14,-0.05)	p≤0.001

†N = Number of patients included in the modified intention-to-treat (mITT) analysis
M: montelukast; PBO: Placebo; LS Mean: Least-Squares Mean; CI: Confidence Interval; SE: Standard Error
References: NDA 20-829/S-017 (Merck: Montelukast Sodium – Seasonal Allergic Rhinitis); Clinical and Statistical Documentation; Section D, Table D-7, Table D-12.

Table 8 Eye Symptoms Domain of the RQoL Questionnaire: Pivotal AR Studies

		No. of Patients		Baseline		Within Treatment Groups, Change from Baseline		Comparison Between Treatment Groups, Change from Baseline	
		M	PBO	M	PBO	M	PBO	LS Mean (95% CI)	p-Value
		n		Mean		LS Mean (95% CI)			
SAR	162	342	347	2.96	3.06	**-0.79** (-0.93, -.65)	**-0.55** (-0.69, -0.41)	**-0.24** (-0.43, -0.05)	0.012
	192	323	329	2.96	2.97	**-0.83** (-0.96, -0.70)	**-0.67** (-0.80, -0.54)	**-0.16** (-0.34, 0.02)	0.085
	235	517	516	3.10	3.21	**-0.86** (-0.97, -0.74)	**-0.67** (-0.79, -0.56)	**-0.19** (-0.35, -0.03)	0.022
PAR	265	974	967	2.52	2.62	**-0.77** (-0.86, -0.69)	**-0.63** (-0.71, -0.55)	**-0.14** (-0.25, -0.04)	0.008

M = montelukast; PBO = Placebo
*Evaluated on a 7-point scale [0 (very much better) to 6 (very much worse)]

4.3 Treatment Consistency and Persistency

The clinical efficacy of montelukast for the relief of AR symptoms was consistent without regard to factors such as gender, age, ethnicity, history of allergic conjunctivitis, or timing of administration. The treatment effect persisted over the entire 24-hour (daytime and nighttime) period and throughout the entire treatment course.

4.4 Global Evaluation of AR (GEoAR)

The overall clinical relevance of AR treatment has been measured by the patient self-rated Global Evaluation of AR (GEoAR), in which patients were asked to answer one question, "Compared to when I entered the study, my allergic symptoms are …," using a 7-point scale ranging from 0 (very much better) to 6 (very much worse). The GEoAR provides a simple overall measurement of the patient-perceived benefit of the therapy. Results of the patient GEoAR are consistent with previous efficacy measures and provide additional validation of the patient's self-rated symptom scores, as well as the RQoL data. This global measure does not differentiate which symptoms are considered more important than others when patients are determining their overall GEoAR score.

In the pooled analysis of all 3 pivotal SAR studies, as well as in the pivotal PAR study, montelukast demonstrated a significantly better patient GEoAR score as compared to placebo (**Table 9**). Individual study data are included in **Appendix 3**.

Table 9 Patient Global Evaluation of AR (GEoAR): Pooled Pivotal SAR Studies and Pivotal PAR Study

	N†		Mean Treatment Score ± SE		Difference in LS Means (95% CI)	p-Value
	Montelukast	Placebo	Montelukast	Placebo	Montelukast Minus Placebo	
Pooled Pivotal SAR Studies	1186	1197	2.20±0.04	2.52±0.04	-0.31 (-0.43,-0.19)	p≤0.001
Pivotal PAR Study	977	969	2.28±1.29	2.44±1.29	-0.15 (-0.27,-0.04)	p=0.007

† N = Number of patients included in the modified intention-to-treat (mITT) analysis.
LS Means = Least-Squares Mean; SE = Standard Error; CI = Confidence Interval
Reference: NDA 20-829/S-017 (Merck Montelukast Sodium – Seasonal Allergic Rhinitis); Clinical and Statistical Documentation; Section D, Table D-14; and CSR P265.

4.5 Efficacy Conclusion

The efficacy of montelukast has been previously established for AR. The treatment benefits are consistent without regard to age, gender, race or timing of administration, and are persistent across the entire dosing interval and treatment course.

The ocular efficacy of montelukast, and specifically the “itchy/watery eyes” symptoms requested to be included in the OTC label, is supported by the significant improvement observed in the Daytime Eye Symptoms scores of the pooled analysis of all 3 pivotal SAR studies. Results were further supported by similar results observed for the individual scores of “tearing eyes” and “itchy eyes.” Of note, the efficacy of Rx Singulair on eye symptoms (itchy/watery eyes) was similar to that demonstrated on the primary endpoint of nasal symptoms, the basis for approval of Rx Singulair for AR.

The clinical relevance of these efficacy measures is supported by the improvement in the burden of AR ocular symptoms via the eye symptoms domain of the quality of life questionnaire. Overall clinical relevancy of montelukast for the condition of AR is supported by the significantly greater GEoAR scores over placebo, as assessed by patients at the end of study therapy.

Overall, the clinical efficacy data for once-daily montelukast 10 mg FCT support its proposed OTC use for the treatment of AR in adults 18 years of age and older.

5.0 REVIEW OF SAFETY

To support the safety of this product, MCC has provided comprehensive safety data from:

1. The original NDA that led to the asthma approval;

2. The supplemental NDAs that led to the approval of:
   - SAR;
   - PAR;
   - Acute prevention of EIB.

3. Post-marketing databases, including:
   - Merck Adverse Event Reporting and Review System (MARRS);
   - Public sources:
     - FDA Adverse Event Reporting System (AERS);
     - World Health Organization (WHO VigiBase);
     - American Association of Poison Control Centers (AAPCC);
     - Drug Abuse Warning Network (DAWN).
   - Worldwide published literature.

5.1 Safety Data from the Clinical Programs (Adult Studies)

5.1.1 Safety Data from the Original NDA for the Asthma Indication

The safety profile of montelukast is based on data from 10 Phase IIb/III double-blind efficacy studies of asthma in adults (n= 1955 montelukast-treated patients) and from long-term (2 years and longer) safety extensions (3 studies in adults; [n= 622 montelukast-treated patients]) (**Table 10**). Additional confirmatory safety data, at doses up to 90 times the proposed OTC dose, are discussed in **Section 5.1.1.1.**

Table 10 Summary of Montelukast Program for Asthma in Adults and Adolescents (15 Years +)

Study Type (Number of Studies) Protocol Numbers	Total Duration	Total Daily Montelukast Dose	Number of Subjects			Total Subjects Randomized
			Montelukast	Placebo	Active Comparator / Open-Label	
Phase I/IIa Studies (31)[1] 002, 003, 004, 005, 006, 007, 008, 010, 011, 012, 013, 014, 017, 018, 021, 023, 026, 028, 033, 034, 035, 045, 047, 048, 050, 051, 053, 055, 057, 058, 060 (Refs. D-1 to D-31)	1 day to 8 weeks	0.4 to 900 mg	575	335	44	733[2]
Phase IIb/III Studies (10)[3]	3 to 16 weeks	2 to 200 mg	1955	1180	251	3386
Phase IIb Studies: 009, 025 (Refs. D-32; D-35)	3 to 6 weeks	2 to 200 mg	497	127	0	624
Phase III Studies: 015, 020, 029, 031, 042, 046, 056, 059 (Refs. D-33; D-34; D-36 to D-41)	4 to 16 weeks	10 mg	1458	1053	251	2762
Extension Studies[4] 009, 020, 031 (Ref. D-42)	Up to and >2 years	10 to 200 mg	622[5]	0	244[6]	
ALL ADULT STUDIES (41)			**2606[7]**	**1515**	**377[8]**	**4119[2]**

[1] Eighteen late- to post-pubertal (Tanner Stages IV or V) adolescents (age 12 to 17 years) participated in Protocol 021. Include Protocols 033, 045, 057 using an intravenous formulation.

[2] In the Phase I/IIa Studies, subjects received more than one treatment in crossover studies; therefore, the sum of the number of "Subjects Treated" is greater than the "Total Subjects Randomized."

[3] Including the Primary Studies, Protocols 020 and 031.

[4] Subjects in the Extension Studies are already accounted for in "Phase IIb/III Studies."

[5] Seventy-six of the 622 subjects were treated with montelukast for the first time in the Protocol 031 extension (these subjects had received placebo previously in the double-blind efficacy trial).

[6] Eighty-two of the 244 subjects were treated with beclomethasone control for the first time in the Protocol 031 extension (these subjects had received montelukast or placebo in the double-blind efficacy trial).

[7] Includes all subjects treated with montelukast in Phases I/IIa (n=575) and IIb/III Studies (n=1955) plus n=76 subjects in the Extension Studies previously described in Footnote 5.

[8] Includes all subjects treated with active comparator/open-label control in Phases I/IIa (n=44, loratadine in Protocol 017) and IIb/III Studies (n=251, beclomethasone in Protocol 020) plus subjects in the Extension Studies (n=82) previously described in Footnote 6 (Source: NDA 20-829, ISS, Table D-37)

On a cumulative basis, approximately 550 patients were continuously treated for at least 6 months, 250 for at least one year, and 21 patients for at least two years (**Table 11**). Total continuous exposure to study therapy was defined as the longest continuous interval without protocol-defined placebo washout periods or protocol-defined off-drug time.

Table 11 Number of Subjects by Duration of Total Continuous Exposure to Montelukast (Any Dose, All Treatment Periods): All Asthma Study Subjects 15 years +

<6 Months	≤6 Months to <1 Year	>1 Year to <2 Years	≥2 Years	Total
2062	291	232	21	2606

(Source: NDA 20-829, ISS, Table D-40)

For all studies involving subjects 15 years and older, the frequency of clinical AEs was similar between montelukast and placebo (**Table 12**). Withdrawals due to AEs were higher in the placebo group, mostly due to asthma-related events. One death, the result of a motor vehicle accident (subject was a passenger), occurred in the montelukast treatment group.

Table 12 Clinical Adverse Experiences Summary: Adult Primary and Phase IIb/III Asthma Studies

	Primary Studies		Phase IIb/III Studies (Including Primary)		
	Placebo (N = 530)	Montelukast (N = 795)	Placebo (N = 1180)	Montelukast (N = 1955)	Beclomethasone (N = 251)
Number (%) of patients with one or more adverse experiences postrandomization	394 (74.3)	561 (70.6)	841 (71.3)	1299 (66.4)	160 (63.7)
with drug-related adverse experiences	41 (7.7)	82 (10.3)	113 (9.6)	211 (10.8)	31 (12.4)
with serious adverse experiences	5 (0.9)	8 (1.0)	17 (1.4)	19 (1.0)	1 (0.4)
with serious drug-related adverse experiences	0	0	0	0	0
withdrawn from therapy due to adverse experiences	23 (4.3)	17 (2.1)	61 (5.2)	73 (3.7)	5 (2.0)
withdrawn from therapy due to a serious adverse experience	1 (0.2)	5 (0.6)	3 (0.3)	11 (0.6)	1 (0.4)
withdrawn from therapy due to a drug-related adverse experience	4 (0.8)	5 (0.6)	13 (1.1)	14 (0.7)	2 (0.8)
Deaths	0	1 (0.1)	0	1 (0.1)	0
This table does not include those adverse experiences that occurred before randomization.					

(Source: NDA 20-829, ISS, Table D-48)

The most frequent AEs in the Primary and Phase IIb/III studies were upper respiratory infection, asthma and headache. No drug-related SAE was ascribed to montelukast treatment.

In regards to laboratory AEs, discontinuation rates with montelukast therapy were less than placebo (**Table 13**), with all subject discontinuations due to positive serum pregnancy tests, except 1 (placebo arm) due to an increased ALT.

Table 13 Number of Patients (Rate) Discontinued due to Laboratory AEs: Adult Primary and Phase IIb/III Asthma Studies

Treatment Group	Adult Primary and Phase IIb/II Studies
Placebo	6 (0.5%)
Montelukast	4 (0.2%)

Source: NDA 20-829, Section D. Clinical Efficacy and Safety, D-247

5.1.1.1 Large Safety Margin Assessed in Dose-Ranging Clinical Trials

In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences.

Montelukast was generally well-tolerated when administered as 200 mg daily for up to 22 weeks in 19 patients with asthma. The most frequently reported AEs were upper respiratory infection (7) and headache (8); headache was the most commonly reported drug-related AE. There were 2 SAEs ("sprain, shoulder" and "neoplasm, breast, malignant"), considered not related to study medication. Two patients discontinued due to AEs regarded as not related to study medication [breast cancer (1); elevated AST (1)].

Montelukast was also well-tolerated when administered in doses up to 300 mg t.i.d. for 7.33 days in 6 healthy, male subjects. The most frequently reported AEs were headache (2) and bruising (2). No SAEs were reported during this study. Drug-related AEs included headache (1), dry mouth (2) and quadriceps ache (1). One subject (placebo group) discontinued from the study due to an elevated white blood cell count associated with an upper respiratory tract infection.

The safety profile, demonstrated at up to 90 times the proposed OTC dose, is an important factor when considering a product for OTC availability.

5.1.2 Safety Data from the SAR Supplemental NDA

A supplement to the original Rx NDA provided data to support subsequent approval for the SAR indication. Eight multicenter, double-blind, randomized, placebo-controlled clinical trials (Phase IIb/III) contributed safety information for the treatment of patients with SAR, with over 2,000 adult and adolescent patients ages 15 years and older receiving montelukast during the trials. The most frequently reported AEs among all treatment arms were headache and upper respiratory infection.

The number of patients who discontinued study therapy due to an AE was similar across treatment groups (21 [1.2%] and 16 [1.0%], in the montelukast and placebo

treatment groups, respectively) (**Table 14**). Upper respiratory infection was the AE that most frequently resulted in discontinuation of study therapy in both groups (0.2% and 0.3%, in the montelukast and placebo treatment groups, respectively).

Table 14 Clinical Adverse Experience Summary: Pooled SAR Phase II/III Studies

Number (%) of subjects	Montelukast (N=1751)		Loratadine (N=1616)		Placebo (N=1557)	
	n	(%)	n	(%)	n	(%)
With one or more adverse experiences	319	(18.2)	327	(20.2)	293	(18.8)
With no adverse experience	1432	(81.8)	1289	(79.8)	1264	(81.2)
With drug-related† adverse experiences	72	(4.1)	95‡	(5.9)	65	(4.2)
With serious adverse experiences	1	(0.1)	0	(0.0)	5§	(0.3)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	21	(1.2)	15	(0.9)	16	(1.0)
Discontinued due to drug-related adverse experiences	3	(0.2)	6	(0.4)	2	(0.1)
Discontinued due to serious adverse experiences	1	(0.1)	0	(0.0)	2	(0.1)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.

‡ Notable difference between loratadine and placebo: estimated difference and 95% confidence interval (CI) of 1.7% (0.2, 3.2). Notable difference between montelukast and loratadine: estimated difference and 95% CI of 1.8% (-3.3, -0.3).

§ Notable difference between loratadine and placebo: estimated difference and 95% CI of -0.3% (-0.7, -0.0). Although a subject may have had 2 or more clinical adverse experiences, the subject is counted only once in a category. The same subject may appear in different categories.

(Source: NDA 20-829/S-017, ISS, Table E-6)

Laboratory AEs occurred infrequently in the adult pooled Phase II/III studies but were reported at least once from 10 (0.6%) and 16 (1.0%) subjects in the montelukast and placebo treatment groups, respectively. The most frequent drug-related laboratory AE was “ALT increased,” reported in 6 (0.3%) and 6 (0.4%) subjects in the montelukast and placebo treatment groups, respectively.

There were no discontinuations from study therapy due to laboratory AEs and no serious laboratory AEs were reported in the adult SAR studies.

5.1.3 Safety Data from the PAR Supplemental NDA

The supplemental NDA to support approval for the PAR indication included data from 2 studies: the initial and pivotal PAR studies. The PAR program randomized a total of 3,357 adult and adolescent patients ages 15 years and older, of whom, 1,632 received montelukast. Pooled data from the initial and pivotal PAR studies

demonstrated the safety and tolerability profile of montelukast is consistent with previous experience in asthma clinical studies.

In the PAR program, no clinically important differences between montelukast and placebo in the incidence of clinical or laboratory AEs were observed (**Table 15**). Similarly, no serious drug-related AEs and no AR-specific safety concerns were associated with montelukast in this population.

Table 15 Clinical Adverse Experience Summary: Pooled PAR Studies

	Montelukast 10 mg (N=1632)		Placebo (N=1603)	
Number (%) of subjects:	n	(%)	n	(%)
With one or more adverse experiences	511	(31.3)	519	(32.4)
With no adverse experience	1121	(68.7)	1084	(67.6)
With drug-related adverse experiences†	75	(4.6)	79	(4.9)
With serious adverse experiences	6	(0.4)	4	(0.2)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	58	(3.6)	58	(3.6)
Discontinued due to drug-related adverse experiences	4	(0.2)	9	(0.6)
Discontinued due to serious adverse experiences	2	(0.1)	2	(0.1)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.

(Source: NDA 20-829/S-033, ISS, Table 2.7.4:5)

The most common AEs between treatment groups were upper respiratory infection (2.8% placebo, 3.9% montelukast) and headache (4.5% placebo and 3.7% montelukast). Upper respiratory infection was also the most common clinical AE leading to study discontinuation (0.6% placebo, 0.9% montelukast). A total of 10 nonfatal clinical SAEs were reported. Besides pregnancies, SAEs reported in the montelukast arm included laceration (1), dehydration (1), anxiety disorder (1), joint injury (1) and asthma (1). No subject deaths occurred in the PAR studies

5.1.4 Somnolence in SAR and PAR Clinical Studies

Although somnolence was not expected to be a safety concern with anti-leukotrienes, somnolence-related AEs were examined in detail in the SAR and PAR clinical development program databases because of its association as a safety concern with some currently approved OTC therapies (e.g., many antihistamines) for AR. To accomplish this, the Merck & Co., Inc. clinical dictionary was carefully reviewed to identify somnolence-related AE terms. In SAR studies overall, somnolence-related AEs were reported in 5/1746 (0.3%) and 10/1547 (0.6%) subjects in the montelukast and placebo treatment groups, respectively. None of the somnolence-related AEs occurred more frequently in the montelukast treatment group than in the placebo treatment group. In the pooled PAR studies, somnolence-

related AEs were reported in 12/1620 (0.7%) and 17/1586 (1.1%) subjects in the montelukast and placebo treatment groups, respectively. Altogether, somnolence-related AEs occurred slightly less frequently with montelukast than with placebo in controlled trials of both SAR and PAR clinical programs. The incidence of somnolence and somnolence-related AEs with montelukast 10 mg is similar to that seen with placebo.

5.1.5 Safety Data from the EIB Supplemental NDA

The montelukast clinical development program for acute prevention of EIB included 2 pivotal studies in which113 patients were randomized (109 received montelukast as a single 10 mg dose). In these studies, AEs were infrequent; 9.2% and 8.4% of subjects had one or more AEs during the montelukast and placebo treatment periods, respectively (**Table 16**).

- Headache occurred more frequently in the placebo group (2.8% versus 0.9% in the montelukast group);
- Nausea occurred more frequently in the montelukast group (1.8% versus 0.9% in the placebo group);

Two subjects in the montelukast arm discontinued study therapy due to one AE each; asthma (1) and influenza (1). Furthermore, no SAEs, laboratory AEs or deaths occurred during these studies.

Table 16 Clinical Adverse Experience Summary: Pooled Pivotal EIB Studies

	Montelukast (N=109)		Placebo (N=107)	
Number (%) of subjects:	**n**	**(%)**	**n**	**(%)**
With one or more adverse experiences	10	(9.2)	9	(8.4)
With no adverse experience	99	(90.8)	98	(91.6)
With drug-related adverse experiences†	3	(2.8)	2	(1.9)
With serious adverse experiences	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	2	(1.8)	0	(0.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related. (Source: NDA 20-829/S-036, ISS, Table 2.7.4:3)

Cumulatively, across all development programs, clinical trials have shown montelukast 10 mg to be generally well tolerated in adults.

5.2 Addressing Warnings and Precautions in Rx Labeling

The Rx Singulair label lists six *Warnings and Precautions* related to: 1) acute asthma, 2) concomitant corticosteroid use for asthma, 3) aspirin-sensitive asthma, 4) systemic eosinophilic conditions in patients with asthma, 5) phenylketonuria, and 6) neuropsychiatric events. The warning about phenylketonuria is specific to the chewable-tablets formulation which contains aspartame and, therefore, is not relevant to the Singulair Allergy film-coated tablet.

Even though this proposed OTC switch is intended only for adults with AR, the first four warnings warrant discussion due to the high comorbidity of asthma and allergy.

The first three warnings, acute asthma, concomitant corticosteroid use for asthma, and aspirin-sensitive asthma, apply to the management of asthma while under the care of a physician. MCC has clearly labeled the proposed Singulair Allergy product as being only for the treatment of AR, and not for the treatment of asthma. Specific elements of the OTC labeling related to this are listed below.

- "This product is only for allergies. Do not use to treat asthma."
- "Asthma can be a life-threatening condition, and you should follow your doctor's directions."
- "When using this product, if you are currently taking asthma medicines, do not stop taking them."

The OTC development program has demonstrated that these labeling elements are well understood by consumers. (Results of these studies are detailed in **Section 8.0**). The proposed OTC labeling is detailed in **Section 7.0.**

The fourth warning (quoted below from the Rx label) refers to patients with asthma who may present with systemic eosinophilia, and was added based on post-marketing events.

> *In rare cases, patients with asthma on therapy with Singulair may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Singulair and these underlying conditions has not been established.*[22]

Because this condition is rare, unpredictable, and most often associated with more severe cases of asthma which may be treated with oral corticosteroids, it is expected that patients who might develop these symptoms will already be under the care of a

physician and, therefore, this warning is not pertinent to the Singulair Allergy OTC label. OTC availability of Singulair Allergy would not be likely to create additional risk of this occurring beyond the risk that already exists in the current prescription environment.

The sixth warning, which pertains to neuropsychiatric events, is applicable regardless of which indication Singulair is used for and, therefore, is relevant to this switch application. This warning was added to the Rx labeling post-marketing and will be discussed in **Section 5.3** below.

5.3 Post-Marketing Safety Data – All Dosage Forms, All Ages (Pediatric and Adults)

The post-marketing safety data provided in this briefing document are composed of the internal Merck safety database (MARRS), external safety databases including AERS, VigiBase, AAPCC, DAWN and literature to cover the period from market introduction to March 31, 2013.

5.3.1 Patient Exposure

As of May 2013, montelukast has been approved in more than 100 countries for allergy and asthma indications. The worldwide distribution for all indications, from market introduction to May 30, 2013, is approximately 24 billion drug units resulting in nearly 66 million patient-treatment years (PTY) of exposure[†].

5.3.2 Review of the Merck Post-Marketing Safety Database

A review of post-marketing data received for montelukast, for all doses and indications, from HCPs, regulatory agencies, and consumers from market introduction to March 31, 2013 was performed. Cumulatively, 46,527 Individual Case Safety Reports (ICSRs) were received. These reports are for all uses of Singulair Rx regardless of indication, formulation or age. The majority of the events in these case reports were non-serious (71%) and reflect events which are currently listed in the Rx Singulair label.

A review of all post marketing data received for montelukast from HCPs, regulatory agencies, and consumers from market introduction to March 31, 2013 identified the following ten most commonly reported events: Headache, Insomnia, Aggression, Nightmare, Rash, Abnormal behavior, Depression, Drug ineffective, Abdominal pain, and Anxiety.

[†] Calculation based on the assumption that each patient takes one tablet or oral granule sachet daily; 24,175,739,095 units/365 days = 66,234,902 PTY.

5.3.2.1 Psychiatric disorders System Organ Class (SOC)

Psychiatric events comprise approximately 25% of all post-marketing ICSRs received for montelukast. The 10 most frequently reported events within this SOC are:

- Insomnia
- Aggression
- Nightmare
- Abnormal behavior
- Depression
- Anxiety
- Agitation
- Suicidal ideation
- Mood altered
- Abnormal dreams

Similar to all reports received for montelukast, the majority (73%) of these ICSRs were non-serious and reflect events which are well-described in the Rx Singulair label.

ICSRs over time

Subsequent to the initial NDA approval, the Rx label has been updated over time to reflect new information obtained from clinical trials and from post-marketing exposure. Of particular interest for this switch application, terms associated with neuropsychiatric events have been added to the Rx Singulair label, as follows:

1999: dream abnormalities, drowsiness, irritability, and restlessness;
2000: insomnia;
2001: seizure, hallucinations;
2002: agitation including aggressive behavior
2007: tremor, depression, suicidal thinking and behavior (suicidality);
2008: anxiousness;
2009: hostility and somnambulism;
2010: disorientation;
2013: memory impairment, disturbance in attention.

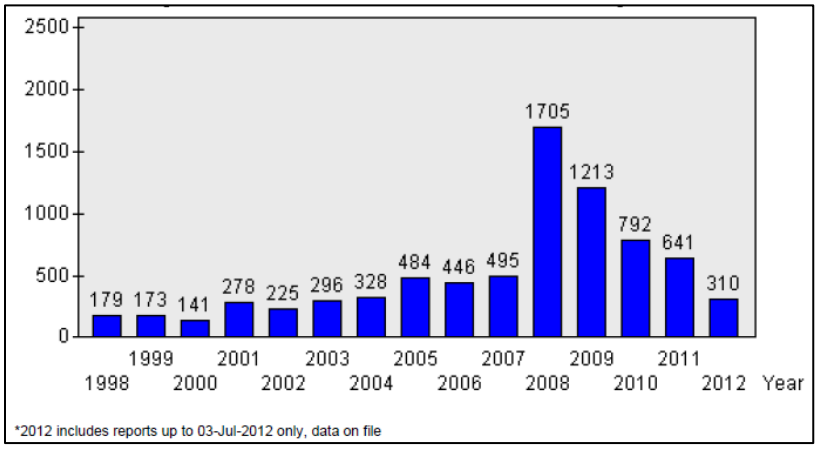
In order to better understand the trend of reports of psychiatric disorders over time, MCC analyzed the number of reports received each year since market authorization.

Following an update to the Rx Singulair label where suicidal thinking and behavior (suicidality) was added to the *Side Effects* section‡, the FDA issued a safety alert in March 2008 entitled "Early Communication About an Ongoing Safety Review of Montelukast (Singulair)"[37] and requested all three manufacturers of leukotriene-modifying agents (Merck, AstraZeneca, and Cornerstone Therapeutics) to conduct analyses of their controlled clinical trial data with regard to behavior and mood-related adverse events (BRAEs). In response to this request, Merck provided the data to FDA and conducted a review of the clinical trial data for specific AEs related to neuropsychiatric events, as described below, and conducted two analyses. Subsequently in 2009, Merck published the results of these analyses that were shared previously with the FDA in two publications (a summary of these two publications can be found in **Appendix 4**).[43,44]

Following the Early Communication by the FDA, a significant increase in reporting of psychiatric disorders was observed in the Merck safety database **(Table 17)**, likely due to stimulated reporting as a result of greater awareness among the general public and health care providers, a phenomenon that has been reported by others.[40] This increase in reporting was also captured in the FDA Adverse Event Reporting System database. Many of these reports were for events that had occurred in years prior to 2008. The number of reports has been declining since the peak reporting in 2008 following the safety alert.

‡ The additions of suicidal thinking and behavior (suicidality) to the Rx label were submitted to FDA in October 2007 and approved by the FDA in March 2008. Then the language was amended to "(including suicide)" after a teleconference with the FDA in March 2008.

Table 17 ICSRs with one or more events in the Psychiatric Disorders SOC by Year (Market Introduction to July 3, 2012)



Source: Figure 1, OTC NDA ISS

In January 2009, after reviewing Merck clinical trial data as well as those of the other two manufacturers (AstraZeneca and Cornerstone Therapeutics), the FDA posted an updated communication, stating:

> *"Although these data do not suggest that montelukast, zafirlukast or zileuton are associated with suicide or suicidal behavior, these clinical trials were not designed specifically to examine neuropsychiatric events."*[39]

Within the same communication, it was stated that:

> *"FDA is continuing to review clinical trials data to assess other neuropsychiatric events (mood and behavior adverse events) related to drugs that act through the leukotriene pathway (montelukast, zafirlukast and zileuton)."*[39]

In June 2009, FDA posted that it completed its review of neuropsychiatric events:

> *"As part of its review, FDA reviewed post-marketing reports and also requested that manufacturers submit all available clinical trials data for these products. The post-market reports of patients on these medications included cases of neuropsychiatric events. Some reports included clinical details consistent with a drug-induced effect. In the clinical trial data submitted by manufacturers, neuropsychiatric events were not commonly observed. However, the available data were limited because the trials were not designed to look at neuropsychiatric events. Sleep disorders (primarily insomnia) were reported more frequently with all three products compared to placebo."*[38]

In light of this conclusion and in agreement with FDA, a statement was added to the Rx Singulair label to indicate that "the clinical details of some post-marketing reports involving montelukast appear consistent with a drug-induced effect."[22]

5.3.2.2 Cumulative Review of all Post-Marketing ICSRs with a Fatal Outcome

A total of 367 ICSRs with a fatal outcome were identified in the most recent review of post-marketing safety submitted to the FDA. **Table 18** provides the most frequently reported AE Preferred Terms (>1% of total terms) related to these cases.

Table 18 AE Preferred Term Associated with the 367 Fatal ICSRs (>1% of Total Events)

SOC Body System	Adverse Event Preferred Term	Number of Adverse Events* (N=916)
Psychiatric disorders	Completed suicide	105
General disorders and administration site conditions	Death	52
Respiratory, thoracic and mediastinal disorders	Asthma	37
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	29
Injury, poisoning and procedural complications	Maternal exposure timing unspecified	28
Injury, poisoning and procedural complications	Toxicity to various agents	20
Psychiatric disorders	Depression	16
Injury, poisoning and procedural complications	Exposure during pregnancy	14
Cardiac disorders	Cardiac arrest	12
Immune system disorders	Allergic granulomatous angiitis	12
Infections and infestations	Pneumonia	12
Injury, poisoning and procedural complications	Overdose	11
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	11

*More than one adverse event may be included in each report.

By the nature of post-marketing reports, information received may be incomplete and inconclusive. The clinical indication was not provided for the majority of these cases (~72%), but when reported, asthma was the predominant indication.

A large variety of concomitant medications also were reported, including common medications for asthma, and potential drugs of abuse such as cocaine, oxycodone, morphine and alcohol, and also other medical conditions. In only a minority of ICSRs (33.5%) was the duration of Singulair use reported, with use longer than 30 days listed most commonly.

Review of ICSRs of *'Completed Suicide' (AE Preferred Term)*

A total of 105 ICSRs with a fatal outcome include a Preferred Term (PT) of "completed suicide" for the time period 1998-2013. From these ICSRs, a total of 298 AEs were reported from the major body systems. In reports with a PT of "completed suicide," the most frequently reported concurrent conditions are listed in **Table 19**.

Table 19 Concurrent Conditions Reported with a PT of *"Completed Suicide"* (>1% of All Events)

SOC Body System	Concurrent Condition PT	Number of Events*
Psychiatric disorders	Depression	16
Injury, poisoning and procedural complications	Toxicity to various agents	12
Injury, poisoning and procedural complications	Overdose	7
Injury, poisoning and procedural complications	Gunshot wound	6
Psychiatric disorders	Mood altered	5
Psychiatric disorders	Personality change	5
Psychiatric disorders	Suicidal ideation	5
Infections and infestations	Pharyngitis	4
Nervous system disorders	Headache	4
Psychiatric disorders	Anxiety	4
Psychiatric disorders	Insomnia	4
Psychiatric disorders	Suicide attempt	4
Respiratory, thoracic and mediastinal disorders	Asphyxia	4

*More than one adverse event may be included in each report.

In the majority of these 105 reports, the clinical indication for montelukast therapy was not provided, but when reported, asthma was the predominant indication.

Concomitant medications reported were diverse, totaling 233 listed drugs. These represent both suspect and non-suspect medications. In only 29.5% of ICSRs was the duration of Singulair use reported, with use longer than 30 days listed most commonly.

5.3.3 Overview of Public Post-Marketing Safety Databases

AERS and WHO VigiBase (ex-U.S.) were reviewed for cases in which montelukast was identified as a suspect medication and/or listed along with other suspect medications. Overall, the spectrum of AEs reported in AERS and WHO VigiBase is consistent with the expected profile of montelukast described in the Rx labeling.

A review of the AAPCC database, which collects information from poison centers regarding individuals exposed to poisoning from medications, did not reveal any new information and showed similar trends in side-effects with each of the montelukast formulations. No formulation-specific side-effects were identified.

DAWN captures data from emergency department (ED) visits that are directly caused by drugs and those in which drugs are a contributing factor but not the direct cause of the visit. No evident pattern of occurrence or distribution of AEs reported from these visits was identified.

Overall, a review of AE reports and safety literature involving the marketed use of montelukast has not raised any safety concerns beyond the information provided in the product labeling.

5.4 Use in Special Populations

Montelukast has no restricted use in special populations and is not contraindicated for any patients as noted in Rx Singulair labeling (direct quotes are italicized).

Geriatric Use

Of the total number of subjects in clinical studies of montelukast, 3.5% were 65 years of age and older, and 0.4% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Review of reported clinical AEs has not identified differences between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The pharmacokinetic profile and oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly but no dosage adjustment in the elderly is required.[22]

Hepatic Insufficiency

The elimination of montelukast was slightly prolonged in patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis compared with that in healthy subjects. As a result of the large therapeutic index and safety margins for montelukast, *no dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency.*[22]

Renal Insufficiency

Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. *No dosage adjustment is recommended in patients with renal insufficiency.*[22]

Pediatric Use

Rx montelukast 10 mg is indicated for ages 15 years and older; the proposed OTC montelukast product is labeled for adults 18 years of age and older. Doses for younger children are 4 and 5 mg depending on age and are delivered in alternate dosage forms (chewable tablet or oral granules).

Extensive pharmaco-toxicologic evaluation, together with clinical safety evaluation from both the asthma and AR development programs of montelukast, are available in children, as described in the Rx label. Based on these data, there appears to be no unique risk regarding use of montelukast in children. Furthermore, inappropriate use of the 10 mg tablet in children is unlikely to present an important safety risk.

Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Teratogenic Effect: No teratogenicity was observed in rats and rabbits at doses approximately 100 and 110 times, respectively, the maximum recommended daily oral dose in adults based on AUCs.

Congenital Abnormalities: The limited number of post marketing ICSRs of pregnancy exposure with montelukast available for analysis suggests an overall birth defect rate similar to the expected rate in the background population. Six spontaneous reports of congenital limb reduction defects have been reported. It is difficult to assess causality from spontaneous reports and available data do not indicate a plausible biological mechanism by which montelukast could cause limb defects. Limb defects have also been reported in infants born to mothers taking other asthma medications[§] (e.g., albuterol). A causal relationship between these events and Singulair has not been established.[22]

5.5 Overdose

No specific information is available on the treatment of overdose with Singulair. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and, in short-term studies, up to 900 mg/day to subjects for approximately a week without clinically important adverse experiences. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

There have been reports of acute overdose in post-marketing experience and clinical studies with Singulair. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of overdose reports. The most frequently occurring adverse experiences were consistent with the safety profile of Singulair and included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.

[§] The National Library of Medicine (NLM) (2010) Retrieved on January 29, 2010 from http://dailymed.nlm.nih.gov/dailymed/about.cfm

5.6 Safety Summary for Singulair Allergy

- From the original analyses of clinical trial data:
  - Across all Phase IIb/III trials for all indications, of more than 6,000 montelukast-treated patients, the AE profile of montelukast was similar to placebo.
  - No mechanism-based AEs have been reported for montelukast, consistent with the physiologic role of leukotrienes.
  - Most relevant for this Rx-to-OTC switch application, the safety of montelukast specifically for the AR indication has been well-studied (more than 3,000 montelukast-treated patients) and shows an AE profile similar to placebo.
  - The short- and long-term (approximately 2 years of continuous treatment) safety profile demonstrates montelukast is generally well tolerated;
  - Montelukast has a very wide safety margin and has been studied in clinical research up to 200 mg per day for 22 weeks, and 900 mg per day for approximately 1 week. These trials have shown a safety profile consistent with the 10 mg FCT.

- From the post-marketing data:
  - The post-marketing safety profile of Singulair has been generally consistent with the safety profile observed during the clinical development program.
  - The majority of events reported was non-serious and reflect events which are well-described in the Rx label.
  - As of 2013, approximately 25% of ICSRs in the MARRS database describe one or more events in the Psychiatric disorders SOC.
  - A significant increase in reporting of psychiatric disorders in the MARRS database starting in 2008 was likely due to stimulated reporting following the safety alert and heightened media awareness.
  - As of 2013, the review of post-marketing events from external databases has not revealed any new safety events beyond what is already provided in the product labeling.
- FDA concluded from its retrospective analyses of clinical trial data and post-marketing reports related to behavior and mood AEs, that:
  - “Although these [clinical trial] data do not suggest that montelukast, zafirlukast or zileuton are associated with suicide or suicidal behavior, these clinical trials were not designed specifically to examine neuropsychiatric events.”[39]

  - "The post-market reports of patients on these medications included cases of neuropsychiatric events. Some reports included clinical details consistent with a drug-induced effect."[38]
  - As a result, the FDA requested that all three manufacturers include a precaution in the drug prescribing information related to neuropsychiatric warnings.

- From the literature review:
  - No new safety events were identified by a literature review.
- Regarding use in special populations:
  - Montelukast has no restricted use in special populations (age, gender, comorbidities), and is not contraindicated for any patients.
- Regarding overdose:
  - AEs in post-marketing reports of overdose up to 1000 mg were consistent with the safety profile of the 10 mg tablet, as listed in the Rx label.

6.0 TOPICS RELEVANT THIS RX-TO-OTC SWITCH APPLICATION

MCC has evaluated the following topics relevant to the Singulair Allergy switch application:

1. Rx Singulair is currently indicated for both allergy and asthma; therefore, there is the potential for off-label use to treat asthma in the OTC setting;
2. The current Rx Singulair label contains several behavior and mood-related warnings that must be clearly communicated to an OTC consumer.

6.1 Potential Off-Label Use to Treat Asthma

Rx Singulair is indicated for AR and asthma. Due to their prior experience with the Rx product, some individuals may potentially use the OTC product off-label to help manage their asthma. This concern about potential off-label use of an OTC product is not unique for Singulair Allergy. As mentioned earlier, many OTC products such as Proton Pump Inhibitors to treat frequent heartburn, NSAIDs to reduce fever and relieve minor aches and pains, and topical antifungals to treat athlete's foot, jock itch, and ringworm remain Rx for higher doses and/or for other indications, such as peptic ulcer disease and erosive esophagitis, rheumatoid arthritis and osteoarthritis, and *tinea versicolor*, respectively. OTC Drug Facts labels direct when to see a doctor for a potentially more serious condition to assure safe use in the nonprescription setting. These products have been used safely in the OTC environment for decades and, yet, do not have specific Drug Facts label warnings against use for labeled Rx indications.

As a result of discussions with the FDA, MCC has taken a different approach as compared to other partial Rx-to-OTC switch applications. Namely, MCC has clearly labeled the proposed Singulair Allergy product as being only for the treatment of AR, and not for the treatment of asthma, and the development program has demonstrated that this is well understood by consumers. The proposed OTC labeling is detailed in **Section 7.0** below.

The OTC label was developed to minimize any potential incremental risk of people with asthma using this product to treat their asthma without the benefit of an HCP. The following safeguards have been incorporated into the Singulair Allergy label to minimize the potential risk of off-label use for asthma in the OTC environment:

- The proposed product name is "Singulair Allergy" which is prominently displayed on the front and side panels;
- The statement "for indoor and outdoor allergies" appears on front panel of the carton;
- The statement "for allergies" appears prominently on the front panel of the carton;

- The statement "**THIS PRODUCT IS ONLY FOR ALLERGIES. DO NOT USE TO TREAT ASTHMA**" is featured above the Drug Fact label in a bright yellow box with bolded, capitalized letters;
- A warning on the Drug Facts label states, "Do not use to treat asthma. Asthma can be a life-threatening condition, and you should follow your doctor's direction;"
- Consumers currently taking asthma medicines are warned to "not stop taking them."

This topic was thoroughly addressed as a key component of the OTC development plan. The Singulair OTC Label Interpretation and Decisions consumer study (SOLID) demonstrated that people with asthma appropriately self-selected not to use Singulair Allergy to treat their asthma. The study also demonstrated that key warnings and directions on the OTC label were well understood. Details of this study can be found in **Section 8.3**.

6.2 Behavior and Mood-Related Changes

The second topic relevant to Singulair Allergy is that behavior and mood-related changes have been reported with Rx Singulair. Therefore, the Rx labeling contains warnings about behavior and mood-related changes. MCC has carefully considered how to communicate to OTC consumers that they should "stop use and ask a doctor" if they experience behavior and mood-related changes.

The current Rx patient package insert warning relative to these potential neuropsychiatric events is as follows:

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - attention problems
  - bad or vivid dreams
  - depression
  - disorientation (confusion)
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - irritability
  - memory problems
  - restlessness
  - sleep walking
  - suicidal thoughts and actions (including suicide)
  - tremor
  - trouble sleeping

For OTC Singulair Allergy, MCC has developed consumer language to communicate these important warnings to consumers in a clear and concise matter. The OTC label was developed to minimize any potential incremental risk of consumers using this product without the benefit of an HCP versus the risks they are already exposed to when using the prescription product. Specifically, the following warnings are included on the OTC Drug Facts label:

Stop use and ask a doctor if

- You experience unexpected changes in behavior, thoughts or mood
- You experience unexpected changes or problems when you sleep

These two warnings were selected after qualitative testing of four label versions, during which it was determined that this language was the most effective to communicate broad categories of symptoms to consumers to convey the spectrum of potential neuropsychiatric events.

Furthermore, MCC has proposed a CIL that will provide more details about these warnings, based on the language from the Rx patient package insert that is currently provided to users of Rx Singulair today (see above).

The following two consumer studies demonstrated that 97% of adults with allergies understood the warnings and 95% of adolescents could interpret the warnings appropriately:

- Label Comprehension Warnings Study (13007) among adults ≥18 years old, with AR;
- Teen Self-Selection and Warning Interpretation Study (13023) among teens, 15-17 years old, with AR;

Additional details of these studies can be found in **Sections 8.4** and **8.5**, respectively.

This topic is also discussed in **Section 9.0**, Benefit and Risk Considerations of OTC Singulair Allergy.

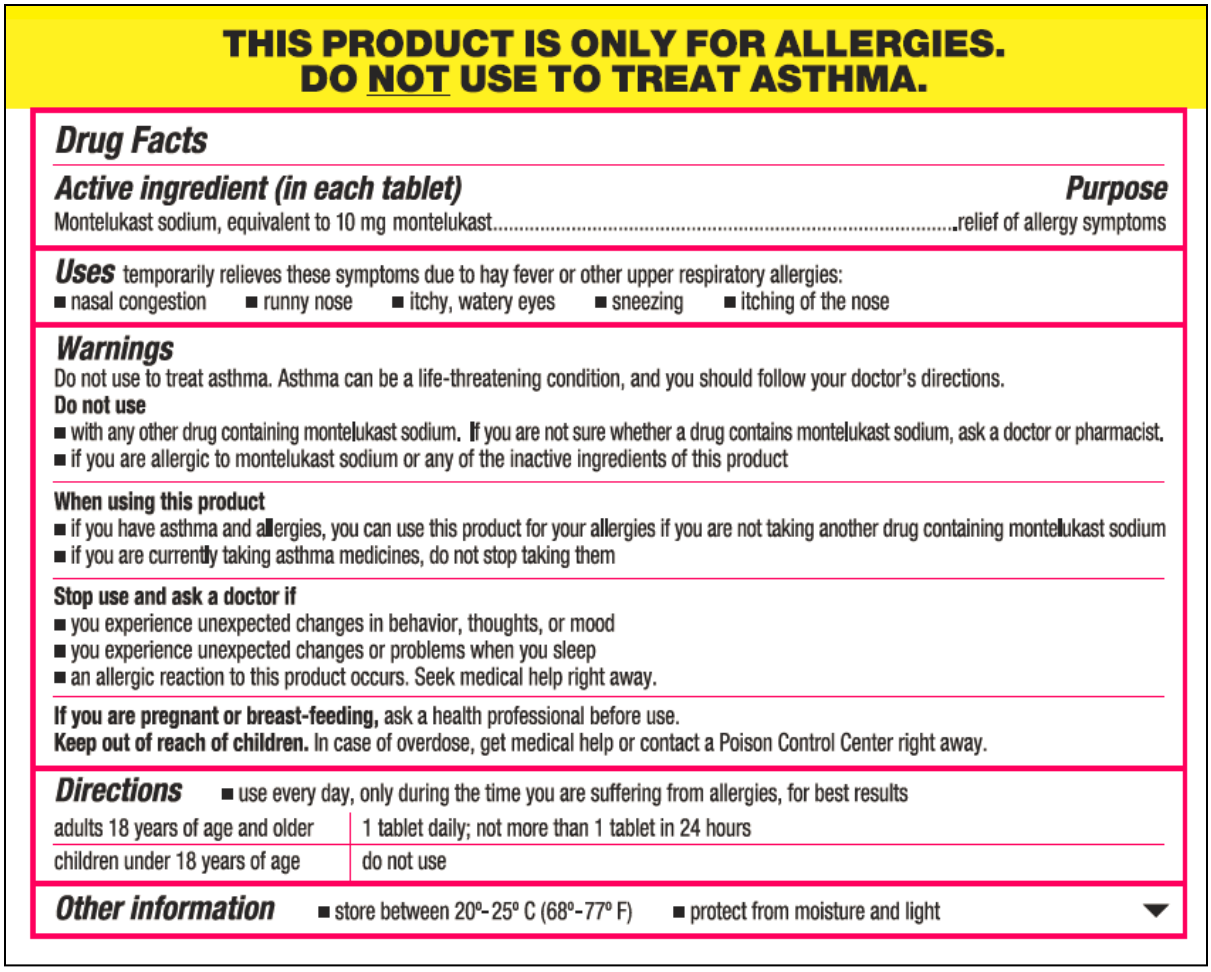
7.0 PROPOSED SINGULAIR ALLERGY LABELING

The proposed OTC labeling for Singulair Allergy consists of two parts. The first is the Drug Facts label, which follows the format codified in the 21 Code of Federal Regulations (CFR) 201.66. The CFR provides very specific rules regarding the format, headings, and types of content for OTC Drug Facts labels. The second part is the CIL to be provided inside the package. The specific content of the Drug Facts label and the CIL was based on:

- OTC first generation antihistamine labeling codified in the Final Monograph 21 CFR Part 341 and OTC labeling approved via the NDA process for the OTC second generation antihistamines (given similarity in target population and symptoms);
- Rx Singulair labeling (both the professional label and the patient package insert);
- Consumer research findings; and
- Advice provided by FDA during the drug development process.

As with any potential switch, the Singulair OTC Drug Facts label was developed to incorporate the most pertinent information needed for consumers to safely use the product without the benefit of an HCP, in consumer-friendly language, and in line with FDA's standard OTC labeling requirements. The OTC allergy category labeling has been on the OTC market for years and, therefore, efforts have been made to align the Singulair Allergy label with labeling for existing products to minimize consumer confusion.

The proposed OTC labeling for Singulair Allergy enables appropriate self-selection, use and de-selection by consumers. Utilizing an iterative process, a comprehensive series of qualitative and quantitative consumer research studies aimed at improving consumer comprehension of the label were completed. As a result of these efforts, the following Drug Facts label has been proposed for Singulair Allergy:



THIS PRODUCT IS ONLY FOR ALLERGIES.
DO NOT USE TO TREAT ASTHMA.

Drug Facts

Active ingredient (in each tablet) — **Purpose**

Montelukast sodium, equivalent to 10 mg montelukast ..... relief of allergy symptoms

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
- nasal congestion
- runny nose
- itchy, watery eyes
- sneezing
- itching of the nose

Warnings

Do not use to treat asthma. Asthma can be a life-threatening condition, and you should follow your doctor's directions.

Do not use
- with any other drug containing montelukast sodium. If you are not sure whether a drug contains montelukast sodium, ask a doctor or pharmacist.
- if you are allergic to montelukast sodium or any of the inactive ingredients of this product

When using this product
- if you have asthma and allergies, you can use this product for your allergies if you are not taking another drug containing montelukast sodium
- if you are currently taking asthma medicines, do not stop taking them

Stop use and ask a doctor if
- you experience unexpected changes in behavior, thoughts, or mood
- you experience unexpected changes or problems when you sleep
- an allergic reaction to this product occurs. Seek medical help right away.

If you are pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions ■ use every day, only during the time you are suffering from allergies, for best results

adults 18 years of age and older	1 tablet daily; not more than 1 tablet in 24 hours
children under 18 years of age	do not use

Other information ■ store between 20°-25° C (68°-77° F) ■ protect from moisture and light

7.1 Consumer Information Leaflet (CIL)

MCC has proposed a CIL that will provide more details about the warnings related to unexpected changes in behavior, thoughts, mood or sleep. This CIL is based on language from the Rx patient package insert that is currently provided to users of Rx Singulair today.

8.0 SINGULAIR ALLERGY OTC DEVELOPMENT PROGRAM

8.1 OTC Development Plan

The currently approved dosage and administration of Rx Singulair for AR treatment is one 10 mg tablet daily for ages 15 years and older. MCC has proposed to label Singulair Allergy only for ages 18+. Many OTC allergy products are approved for children ages 12 and older. However, for Singulair, lower doses of 5 mg and 4 mg are indicated for children under 15. Because 18 and older is an established adult age cut-off for other first-in-class OTC switch products (e.g., Proton pump inhibitors like omeprazole or the weight loss aid orlistat), this age was a logical choice for this new Rx-to-OTC switch targeted only for adults.

The OTC development goals were discussed with the FDA, and three self-selection and/or label comprehension studies were conducted. FDA did not request an Actual Use Study to support this partial OTC switch application because the AR category is well established with many other OTC medications and Singulair Allergy has a similar dosing form and regimen to these already approved products.

The consumer studies addressed the following three goals:

1. To establish that adults with asthma understand that Singulair Allergy should not be used to treat asthma;
2. To demonstrate that the behavior mood-related warnings are well understood by both adults and teens; and
3. To determine that teens understand Singulair Allergy is only to be used by adults 18 years of age and older.

This development plan assessed how populations *not* intended for the proposed Singulair Allergy indication, such as people with asthma and teens with AR, might respond to the label and behavior-related warnings, since Rx Singulair is both an asthma and allergy medication and is indicated for use in people 15 years of age and older.

The first goal was addressed in a pivotal study that assessed whether adults with asthma, with or without AR, interpreted the label correctly, since Rx Singulair is both an asthma and allergy medication. To address the second goal, a study was conducted to determine if adults with AR understood the behavior and mood-related warnings on the Drug Facts label. A third study was conducted in an adolescent population (15-17 years of age) with AR to determine if they understood the age directive not to use this product if less than 18 years of age.

8.2 Summary of Findings

To address these program goals, three consumer research studies were conducted (**Table 20**).

SOLID (Singulair OTC Label Interpretation and Decisions Study), the pivotal targeted combined self-selection and label comprehension study, included three cohorts of asthma subjects:

- **Cohort 1**: people with asthma with or without AR **with prior use** of Singulair
- **Cohort 2**: people with asthma with or without AR **with no prior use** of Singulair
- **Cohort 3**: people with asthma with or without AR who have low literacy skills

This design was undertaken since we believed that prior users of Rx Singulair may react to the OTC product labeling differently than those who were not familiar with Rx Singulair. The results of this study demonstrated that people with asthma, regardless of whether or not they previously used Rx Singulair, can correctly self-select to use or not to use Singulair Allergy based on the label and their own health history. In addition, they also understand the key safety messages indicating Singulair Allergy is not to be used to treat asthma and to not stop using their asthma medications when using Singulair Allergy.

Two additional targeted consumer studies were conducted to specifically evaluate the behavior and mood-related warnings. The first was a label comprehension study among a general population of adults 18 years of age and older with AR. This population was characterized into two subgroups – those with a self-reported doctor diagnosis of depression and those without. The rationale for conducting subgroup analysis of people with depression was that people with AR have a higher rate of depression.

The second consumer study was a combined self-selection and label interpretation study among a general population of adolescents with AR, ages 15-17. Both consumer studies showed that the adults and adolescents understood the behavior and mood-related warnings. The targeted label-comprehension study among adults also showed the warnings were well understood by adults with AR who self-reported ever receiving a doctor diagnosis of depression and also by those who self-reported never having depression.

Table 20 Consumer Studies

Program Goals	Consumer Study	Population
Establish that people with asthma understand that Singulair Allergy should not be used to treat asthma	Pivotal Self-Selection and Label Comprehension Study (SOLID: Singulair OTC Label Interpretation and Decision Study)	Adult ≥18 years old with asthma , with or without AR with prior or no prior use of Singulair (n=820)
Demonstrate behavior warnings are well understood	Label Comprehension Warnings Study (13007)	Adult, ≥18 years old, with AR (n=361)
Determine teens understand that Singulair Allergy is only for adults 18 years +	Teen Self-Selection and Warning Interpretation Study (13023)	Teen, 15-17 years old, with AR (n=350)

It is important to define target thresholds during the planning phase of these studies that follow FDA guidelines to assess success of the key (primary) label messages being communicated and the behaviors elicited. The point estimates and ranges provide an overall measure of comprehension and self-selection decision-making, rather than a binary measure where missing or achieving the target represents failure or success. Scores in these types of studies rarely reach 100% due to many factors such as subject fatigue, interviewer error or interviewer bias, question ambiguity; and degree of attention the subject is giving to the task, when there is often no downside to guessing or responding quickly in this single-visit research study.

8.3 Combined Label Comprehension and Self-Selection Study: Singulair OTC Label Interpretation and Decisions (SOLID)

MCC and FDA corresponded several times between 2007 and 2009 regarding the proposed Singulair Allergy labeling and consumer studies. Using the advice received from FDA, this pivotal study in the OTC switch development program was designed as a combined self-selection/label comprehension study and is summarized below.

8.3.1 Objectives

The primary objectives of the pivotal study, SOLID, a combined self-selection and label comprehension study were to assess the ability of adults with asthma 18 years of age or older to appropriately select to use or not to use Singulair Allergy after reading the package label, based on their own medical history, and to understand comprehension of key asthma related safety messages on the Drug Facts label. In addition, cohorts of prior users and non-users of Rx Singulair were included in order to determine if there would be a difference in scores based on prior knowledge of the prescription product.

8.3.2 Methodology

Study methodology was based on established best practices in consumer research as well as the FDA Guidance for Industry - Label Comprehension Studies for Nonprescription Drug Products (August 2010)[29] and FDA Guidance for Industry – Self-Selection Studies for Nonprescription Drug Products (September 2011, Draft).[30]

Study subjects were recruited using mass media, community outreach flyers, and subject databases that represent a broad cross-section of those who might or might not use the product. Potential subjects were screened over the phone using the inclusion/exclusion criteria, and the exclusion criteria are included in Appendix 2. Qualified subjects were directed to a local market research or clinical research site for a one-on-one interview. In total, 17 market research and clinical research facilities across the U.S. were utilized.

At the research site, subjects were provided the package label for Singulair Allergy to read. When subjects finished reading, study interviewers asked them the self-selection question ("*Is this product appropriate for you, personally, to use or not?")* and follow-up questions to obtain the rationale for their selection decision. Following the self-selection portion of the interview, the Rapid Estimate of Adult Literacy in Medicine (REALM) test was administered to each subject. The REALM is a standardized test with 66 words that each subject reads. Those scoring 60 or below on REALM, are classified as having low literacy skills.

After administration of the REALM, the label comprehension portion of the interview took place and subjects had access to the Singulair Allergy package label throughout the interview. This section of the questionnaire consisted primarily of various scenarios describing possible real-life situations in which other people could find themselves. Study subjects had to make decisions regarding the product's appropriate and inappropriate use in those situations based solely on their understanding of the product label. An example of a scenario question is:

> *"Karen has asthma. She would like to use this product to treat her asthma. According to the product label, is it okay or not okay for Karen to use this product to treat her asthma?"*

All scenario questions were followed by an open-ended question asking the subjects why they gave the answer they did (*"Why do you say that?").* Responses to both questions were considered in scoring of correctness. Finally, a discrepancy probe was utilized to understand the reason for each incorrect self-selection response, and additional profiling questions were asked to understand current asthma management behaviors.

8.3.3 Self-Selection Decision and Mitigation

The key criteria used to classify a self-selection decision as correct or incorrect was based on whether a study subject selected Singulair Allergy to treat his/her AR or not.

The data adjudication process known as "mitigation" was developed a priori according to FDA Draft Guidance for Industry: Self-Selection Studies for Non-Prescription Drug Products, September 2011.[30] It was employed in order to best capture the intent of the primary endpoint of Self-Selection and to identify decision-making that could potentially place consumers at risk.

For additional details on mitigation for SOLID, see **Appendix 3**.

8.3.4 Subject Enrollment

All subjects in the study were self-reported adults with asthma, with or without indoor/outdoor allergies, and had either ever or never used Rx Singulair. There were 3 separate cohorts, as follows:

- **Cohort 1:** General population of adults 18 years of age or older who have asthma (with or without indoor/outdoor allergies) who ever used Rx Singulair - Prior Singulair Experience (n=384)
- **Cohort 2:** General population of adults 18 years of age or older who have asthma (with or without indoor/outdoor allergies) who never used Rx Singulair – No Prior Singulair Experience (n=349)
- **Cohort 3:** Adults 18 years of age or older with asthma with or without indoor/outdoor allergies) who have low literacy skills (who ever or never used Rx Singulair [n=163]). This group includes subjects who have low literacy skills from Cohort 1, Cohort 2 and is augmented with additional low literacy subjects.

Minimum Exclusion Criteria related to past participation and industry affiliation were included (see **Appendix 2** for details).

Table 21 Subject Demographics (SOLID Study)

Total Responded	Cohort 1: GP Asthma; *Ever* Used (n=384)		Cohort 2: GP Asthma; *Never* Used (n=349)		Cohort 3: † Low Literate Asthma (n=163)	
	n	%	n	%	n	%
Subgroup						
Asthma-Only	70	18.2	71	20.3	43	26.4
Asthma & Allergies	314	81.8	278	79.7	120	73.6
Gender						
Male	127	33.1	136	39.0	70	42.9
Female	257	66.9	213	61.0	93	57.1
Age Range						
18 to 24	33	8.6	40	11.5	18	11.0
25 to 34	72	18.8	54	15.5	34	20.9
35 to 44	74	19.3	51	14.6	24	14.7
45 to 54	99	25.8	84	24.1	40	24.5
55 to 64	64	16.7	78	22.3	29	17.8
65 or older	42	10.9	42	12.0	18	11.0
Race						
Caucasian/White	258	67.2	235	67.3	46	28.2
African-American/Black	101	26.3	93	26.6	104	63.8
Native American	2	0.5	1	0.3	--	--
Asian or Pacific Islander	2	0.5	4	1.1	1	0.6
Other	21	5.5	16	4.6	12	7.4
Hispanic Origin						
Yes	28	7.3	17	4.9	14	8.6
No	356	92.7	332	95.1	149	91.4
Education						
Less than High School	10	2.6	15	4.3	55	33.7
Completed High School	69	18.0	69	19.8	47	28.8
Some College/Technical School	144	37.5	155	44.4	56	34.4
Graduated College/Technical School or more	161	41.9	110	31.5	5	3.1
Income						
$0 to $14,999	52	13.5	54	15.5	91	55.8
$15,000 to $24,999	37	9.6	35	10.0	17	10.4
$25,000 to $34,999	38	9.9	47	13.5	15	9.2
$35,000 to $44,999	50	13.0	45	12.9	9	5.5
$45,000 to $64,999	66	17.2	51	14.6	14	8.6
$65,000 to $74,999	32	8.3	34	9.7	5	3.1
$75,000 or more	100	26.0	75	21.5	11	6.7
Refused	9	2.3	8	2.3	1	0.6
REALM Category						
Low Literate	40	10.4	36	10.3	163	100.0
Normal Literate	344	89.6	313	89.7	--	--

†Includes overlap of low literate subjects from Cohorts 1 and 2 (n=76) as well as the additional augment low literate completes (n=87).
Due to rounding percentages may not sum 100%
(--) Indicates a percentage that does not round to 1 or is zero.
Source: Tabulated Data; SDTM Data

8.3.5 Primary Endpoint: Self-Selection

The primary endpoint for the SOLID study was the number of subjects who had a correct overall response for the self-selection decision ("*Is this product appropriate for you, personally, to use or not?")*, post-mitigation.

The primary endpoint would meet the target threshold if the lower bound of the two-sided 95% exact confidence interval for each cohort of general population were above 90% for self-selection.

Cohort 1 subjects (adults with asthma who have ever used Rx Singulair) achieved a correct self-selection score of 91.7% (88.4% lower bound). Cohort 2 subjects (adults with asthma who have never used Rx Singulair) achieved a correct self-selection score of 96.3% (93.7% lower bound). Adults with asthma who have low literacy skills made correct self-selection decisions were comparable to the general population (90.8% self-selection score, 85.3% lower bound).

Of the small percentage of subjects within each cohort who were incorrect self-selectors (Cohort 1= 8.3%, Cohort 2 = 3.7%), the majority demonstrated comprehension of the key warnings on the label (e.g., not to use for asthma, not to stop taking asthma medicine, and use only if 18 years or older), and also described personal asthma management behaviors that suggest they are experienced asthma sufferers who have established relationships with their physicians and utilize appropriate treatment options for acute asthma situations (e.g. albuterol or other asthma rescue medications).

8.3.6 Secondary Endpoint: Label Comprehension of Primary Communication Objectives

The secondary endpoints were the number of subjects who had a correct overall response for each key (primary) label comprehension communication objective (or primary medical risk consideration).

These secondary endpoints would meet the target threshold if the lower bound of the two-sided 95% exact confidence interval for the general population of adults with asthma were above 90% for comprehension.

Additional analyses regarding secondary label comprehension communication objectives (or medical risk considerations of lesser importance) were also performed. Secondary communication objectives were not assigned a threshold target.

Primary Medical Risk Considerations

The general population of subjects with asthma exceeded 90% comprehension on all 3 key (primary) communication objectives and met the lower bound threshold for 2 of the 3 objectives, as shown in **Table 22** below.

Table 22 Analysis of Secondary Endpoint Label Comprehension of Primary Medical Risk Considerations

	Cohort 1 GP Asthma; *Ever* Used N=384			Cohort 2 GP Asthma; *Never* Used N=349		
Objective	**n**	**%**	***LB**	**n**	**%**	***LB**
Do not use to treat asthma	352	91.7	88.4	322	92.3	88.9
Do not stop using asthma medicine	361	94.0	91.2	335	96.0	93.4
Do not use if under 18 years of age	368	95.8	93.3	338	96.8	94.4

**Lower two-sided 95% exact confidence bounds.*
Source: Tabulated Data; SDTM Data

- The key safety warning,"*Do not use to treat asthma,"* achieved comprehension scores in Cohort 1 of 91.7% (88.4% lower bound) and Cohort 2 of 92.3% (88.9% lower bound).
- *"When using this product, if you are taking asthma medicines, do not stop taking them"* achieved comprehension scores in Cohort 1 (people with asthma who have ever used Rx Singulair) of 94.0% (91.2% lower bound) and Cohort 2 (people with asthma who have never used Rx Singulair) of 96.0% (93.4% lower bound).
- Directions for use, *"Do not use if under 18 years of age",* achieved comprehension scores in Cohort 1 of 95.8% (93.3% lower bound) and Cohort 2 of 96.8% (94.4% lower bound).

Secondary Medical Risk Considerations

The three secondary communication objectives which did not have a threshold target, "Okay to use Singulair Allergy to treat allergies along with asthma medicine," "Do not use along with prescription montelukast sodium," and "Ask a doctor or pharmacist if not sure other medicine has montelukast sodium," achieved 88% or higher comprehension score among Cohort 1 subjects and 86% or higher score among Cohort 2 subjects.

8.3.7 Analysis of Self-Selection & Label Comprehension Scores among those who have Low Literacy Skills

Among subjects with asthma who have low literacy skills, 90.8% made an appropriate self-selection decision, which is comparable to the general population score. This is quite good, considering that, commonly, the low literacy population performs more poorly than the general population in label comprehension and self-selection studies.

Seventy-nine percent of subjects with asthma who have low literacy skills understood the key safety warning to not use Singulair Allergy to treat asthma and 88% understood not to stop using asthma medicine. Furthermore, 91% understood not to use Singulair Allergy if under 18 years of age.

For the three secondary medical risk consideration communication objectives "Okay to use Singulair Allergy to treat allergies along with asthma medicine," "Do not use along with prescription montelukast sodium," and "Ask a doctor or pharmacist if not sure other medicine has montelukast sodium," people who have low literacy skills on average achieved 75% comprehension score.

Table 23 Self-Selection & Label Comprehension Scores among those who have Low Literacy Skills

	Cohort 3 People with Asthma & Low Literacy Skills N=163	
	n	**%**
Self-Selection Score	148	90.8
Objective	**n**	**Comprehension Score %**
Primary Medical Risk Considerations		
Do not use to treat asthma	129	79.1
Do not stop using asthma medicine	143	87.7
Do not use if under 18 years of age	149	91.4
Secondary Medical Risk Considerations		
Okay to use SINGULAIR Allergy to treat allergies along with asthma medicine	114	69.9
Do not use along with prescription montelukast sodium	110	67.5
Ask a doctor or pharmacist if not sure other medicine has montelukast sodium	142	87.1

Source: Tabulated Data; SDTM Data

8.3.8 Additional Analysis: Self-Recognition of Asthma Triggers and Appropriate Action in the Event of Acute Asthma Attack

At the end of the interview, a few questions were asked to assess subjects' management of asthma behaviors via open-ended questions (multiple responses permitted). The purpose of this was to determine if people with asthma recognized what triggered their asthma attacks as well as to establish what action they would take in the event of an acute asthma attack.

Results indicated that 97.9% of all study subjects could identify their asthma triggers (58.8% outdoor allergens, 41.8% indoor allergens, 31.8% exercise/exertion, etc.), which enables them to either avoid or manage their triggers. Also, 99% of all study

subjects with asthma self-reported they knew what action to take should an asthma attack occur: 59.5% would use an inhaler; 35.2% would see/contact a doctor or go to hospital; and 11.7% would use a nebulizer or breathing treatment. When asked about the frequency of seeing a physician about their asthma, 49% self-reported seeing their physician at least twice in a year, 48% once a year or less frequently and the remaining 3% were either uncertain or provided a different response. In addition, on average they reported taking 3 prescription allergy/ asthma products in the past 12 months. In summary, the subjects in this study reported that they would take an appropriate action should an acute asthma attack occur.

Post-Study Analysis: Combined Results of Cohort 1 and Cohort 2

In order to understand how general population of people with asthma would self-select, regardless of prior Singulair use, Cohorts 1 and 2 were combined in a post-hoc analysis. This analysis showed that, overall, the general population of subjects with asthma were able to make correct self-selection decisions about whether or not Singulair Allergy was appropriate for their use (93.9% correct self-selection score, 91.9% lower bound).

Among the combined population, subjects understood they should not use this product to treat their asthma (92.0% correct comprehension), they should not stop taking their prescribed asthma medications when using this product (95.0% correct comprehension), and they should not use this product for children under 18 years of age (96.3% correct comprehension).

Post-Study Analysis: People with Asthma and Allergy vs. People with Asthma Only

We analyzed how people who had asthma-only would self-select versus those who have both AR and asthma. The results show that 90.8% of people with asthma-only would appropriately self-select not to use this product and 94.6% of people who have asthma with comorbid AR would appropriately self-select in accordance with the product label.

Overall, comprehension scores above 90% for the key (primary) messages (do not use to treat asthma and do not stop taking asthma medication when taking Singulair Allergy) were achieved by those who reported suffering from both AR and asthma and those who reported experiencing asthma only, regardless of their previous Rx Singulair use.

8.3.9 Summary

The results of the SOLID study demonstrated that subjects with asthma appropriately self-selected to use or not use Singulair Allergy based on their personal medical history and understand that Singulair Allergy is not for treatment of asthma. In addition, subjects with asthma understood not to stop taking their asthma medications when using Singulair Allergy.

Furthermore, subjects report an understanding of what triggers their asthma and the actions that they should appropriately take in the event of an emergent asthma attack.

8.4 Label Comprehension Warning Study among Adults

8.4.1 Background

After the SOLID study was completed, MCC added warnings related to behavior and mood-related changes to the Drug Facts label. As a result, four label versions with six warnings were developed and qualitatively tested with consumers in an iterative manner to assess and identify phrases that would succinctly communicate the spectrum of behavior-related events currently listed in the Rx Patient Information Leaflet. Results suggested that, "S*top use and ask a doctor if you experience unexpected changes in behavior, thoughts, or mood*" and "S*top use and ask a doctor if you experience unexpected changes or problems when you sleep*" were the most effective warnings tested. These warnings were subsequently tested in a quantitative Label Comprehension Warnings Study among adults with AR. The study included a subgroup of subjects who self-reported ever receiving a doctor's diagnosis of depression and a subgroup of subjects with no prior doctor's diagnosis of depression.

8.4.2 Objectives

The primary objective of this study was to measure comprehension of two behavior- and mood-related warnings on the Drug Facts label among adults 18 and older with AR, both with and without a self-reported physician's diagnosis of depression. Individuals experiencing depression were included at the request of FDA, to test their comprehension of warnings, even though depression is not contraindicated on the Rx label. The specific warnings that were tested are as follows:

Warnings:

Stop use and ask a doctor:

- if you experience unexpected changes in behavior, thoughts, or mood;
- if you experience unexpected changes or problems when you sleep.

In addition to the primary objective, the following two additional communication objectives were explored to minimize bias by only focusing the subject on one section of the label.

Use: *Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: nasal congestion; runny nose; itchy, watery eyes; sneezing; itching of the nose*.

Directions: *Take 1 tablet daily; not more than 1 tablet in 24 hours.*

8.4.3 Methodology

Study subjects were recruited from research site databases that were developed by obtaining contact information from various community outreach efforts in the general population and interviewed at 10 market research facilities across the U.S. Each qualified subject completed the REALM assessment and was then provided the Singulair Allergy package label to read. When subjects finished reading the label, the label comprehension interview, which consisted of scenarios describing possible real-life situations in which subjects had to make decisions related to the warnings, was administered. For each scenario, a follow-up question *("Why do you say that?")* was also asked to assess the rationale for the response. An additional clarifying question was asked if the subject mentioned "side effect(s)" in his or her response to either of the primary objectives. This clarifying question was asked to better understand what the term "side effect(s)" meant to the subject.

Lastly, additional profiling questions were asked to better understand the subject's experience with indoor/outdoor allergies and other conditions, as well as questions inquiring about previous awareness of Rx Singulair and product usage.

8.4.4 Subject Enrollment

Two separate cohorts were tested:

- **Cohort 1**: General population 18 years of age or older who have AR (n=361), divided into two sub-groups:
  Subgroup 1: self-reported ever having doctor diagnosis of depression (n=82).
  Subgroup 2: self-reported never having doctor diagnosis of depression (n=270).

- **Cohort 2**: Adults 18 years of age or older who have low literacy skills and have AR (n=151). This includes subjects from Cohort 1 (n=32) who have low literacy skills and a supplemental sample of adults with allergies (n=119) to augment the total low literacy study population.

Minimum Exclusion Criteria related to past participation and industry affiliation were included. See **Appendix 2** for details.

Table 24 Subject Demographics (Label Comprehension Warning Study among Adults)

Total Responded	Cohort 1: GP Allergies (n=361)		Cohort 2: † LL Allergies (n=151)	
	n	%	n	%
Subgroup				
Allergies, with Depression	84	23.3	38	25.2
Allergies, No Depression	277	76.7	113	74.8
Gender				
Male	163	45.2	80	53.0
Female	198	54.8	71	47.0
Age Range				
18 to 24	26	7.2	12	7.9
25 to 34	47	13.0	24	15.9
35 to 44	52	14.4	37	24.5
45 to 54	82	22.7	35	23.2
55 to 64	91	25.2	25	16.6
65 or older	63	17.5	18	11.9
Race				
Caucasian/White	286	79.2	33	21.9
African-American/Black	54	15.0	88	58.3
Native American	3	0.8	2	1.3
Asian or Pacific Islander	5	1.4	2	1.3
Other	13	3.6	26	17.2
Hispanic Origin				
Yes	16	4.4	28	18.5
No	345	95.6	123	81.5
Education				
Less than High School	8	2.2	58	38.4
Completed High School	58	16.1	49	32.5
Some College/Technical School	143	39.6	36	23.8
Graduated College/Technical School or more	152	42.1	8	5.3
Employment Status				
Employed full-time	135	37.4	40	26.5
Employed part-time	50	13.9	17	11.3
Self-Employed	31	8.6	8	5.3
Unemployed	29	8.0	44	29.1
Stay at Home Parent/Homemaker	19	5.3	5	3.3
Student	16	4.4	4	2.6
Retired	72	19.9	16	10.6
Disabled	9	2.5	17	11.3
REALM Category				
Low Literate	32	8.9	151	100.0
Normal Literate	329	91.1	0	--

Source: Tabulated Data; SDTM Data

† **Cohort** 2 includes of n=32 low literate subjects from the GP (Cohort 1) and n=119 subjects recruited as an augment of low literate subjects.

(--) Indicates a percentage that does not round to 1 or is zero.

8.4.5 Primary Endpoint

The primary endpoint was the number of subjects who had a correct overall comprehension for each of the two key (primary) communication objectives, which were the warnings listed under the Drug Facts label section "*Stop use and ask a doctor:"*

1. "if you experience unexpected changes in behavior, thoughts or mood"
2. "if you experience unexpected changes or problems when you sleep."

The primary endpoints would meet the threshold if the lower limit of the two-sided 95% exact confidence interval for general population with AR were greater than 90% for each primary objective.

In the general population of adults with AR, the warning, "*stop use and ask a doctor if you experience unexpected changes in behavior, thoughts or mood"* achieved overall comprehension of 97.5% (95.3% lower bound), and *"Stop use and ask a doctor if you experience unexpected changes or problems when you sleep",* achieved overall comprehension of 97.0% (94.6% lower bound).

8.4.6 Label Comprehension of Additional (Secondary) Communication Objectives

The two secondary communication objectives, which did not have a threshold target, achieved 97% or higher comprehension scores among Cohort 1 subjects and 87% or higher scores among Cohort 2 subjects.

Uses: *temporarily relieves these symptoms due to hay fever or other respiratory allergies: nasal congestion; runny nose; itchy, watery eyes; sneezing; itching of the nose.*

Directions: *take one tablet daily; not more than 1 tablet in 24 hours.*

8.4.7 Additional Analyses

Both sub-groups in the general population of adults 18 years and older with AR, those who self-reported *ever* having a doctor diagnosis of depression and those who self-reported *never* having depression, achieved 96% or higher comprehension scores for the two behavior and mood-related warnings.

An additional analysis was conducted among subjects that have lower literacy skills and they achieved 86% or higher comprehension score for both of these warnings.

8.4.8 Summary

The results of this study demonstrated that subjects 18 years of age or older with AR, regardless of whether they had depression or not, understood the two behavior

and mood-related warnings on the Singulair Allergy label, and also clearly understood the product's uses and directions for use.

8.5 Self-Selection and Warning Interpretation among Adolescents

8.5.1 Background

Rx Singulair 10 mg is currently indicated for patients 15 years of age and older. The proposed Singulair Allergy product is labeled for adults ages 18 years or older. In order to assess the potential for misuse, FDA recommended a self-selection and label comprehension study for adolescents, ages 15-17. A targeted study among adolescents to assess appropriate self-selection as well as interpretation of two behavior and mood-related warnings was designed and is summarized below.

8.5.2 Objectives

The objectives of this targeted self-selection and warning interpretation study among adolescents were as follows:

1. The ability of adolescents 15 -17 years old to appropriately self-select not to use Singulair Allergy based on the labeled age or other contraindications.
2. To determine what action adolescents would take should they experience a mood or behavior-related adverse event in case they were to use the product against the label directive. This was done by asking the open ended question, "If you were taking this medicine and started feeling different than you usually do, what, if anything, would you do?" Their verbatim responses were evaluated to determine if they reflected a "safe intended" action. This is defined as a response in which the adolescent subject would communicate a potential drug-related effect to a parent, family member, doctor or pharmacist, or would stop use of the drug.
3. To determine the ability of adolescents to accurately interpret the two behavior-related warnings. This was accomplished by asking adolescents open-ended question regarding the meaning of the phrases in the two behavior and mood-related warnings.

8.5.3 Subject Enrollment

The study was carried out among a general population of adolescents 15-17 years of age who have AR (n=350). The general population that was enrolled included subjects with low literacy skills or subjects with comorbid conditions (depression or asthma) but there was no augmented recruitment.

Minimum Exclusion Criteria related to past participation and industry affiliation were included. See **Appendix 2** for details.

Table 25 Adolescent Subject Demographics

Total Responding	Cohort 1: GP Adolescents with Indoor/Outdoor Allergies n=350	
	N	%
Gender		
Male	181	51.7
Female	169	48.3
Age		
15	126	36.0
16	118	33.7
17	106	30.3
Race		
Caucasian/White	261	74.6
African American/Black	56	16.0
Native American	3	0.9
Asian or Pacific Islander	6	1.7
Other	24	6.9
Hispanic Origin		
Yes	32	9.1
No	318	90.9
Education		
8th Grade	4	1.1
9th Grade	43	12.3
10th Grade	127	36.3
11th Grade	119	34.0
12th Grade	57	16.3
REALM Category		
Low Literacy	90	25.7
Normal Literacy	260	74.3

Source: Tabulated Data Dance Adolescent SS/WI #13023 (Banner 1); SDTM Data
Note: Due to rounding, percentages may not sum to 100%.

8.5.4 Methodology

Parents or guardians of adolescents 15-17 years of age from 10 geographically dispersed markets in the U.S. were screened to determine if their adolescent was eligible to participate in this study. The eligible adolescents with AR were accompanied by their parents or guardians to the market research facility for one-on-one interviews. Each adolescent was interviewed in a room separate from his/her parent or guardian. The parent or guardian provided the adolescent's medical history.

To address the first objective, adolescent subjects were given a Singulair Allergy package label to review and then asked the self-selection question ("*Is this medicine Okay for you to use?")* and a follow-up question (*Why do you say that*?) to obtain the rationale for their selection decision. Subjects who indicated the product would be okay for them to use were asked the additional questions, "*What, if anything, would you use this product to treat?"* and "Y*ou said that this product would be okay for you to use, would you be more likely to take this on your own or would you ask someone first?"* Subjects who indicated they would ask someone first, were further probed, "*Who would you ask?*"

To address the second objective, after the self-selection portion of the interview, the interviewer asked an open-ended question to gather information about what action the adolescent subjects would take if they started to feel different while using this product ("*If you were taking this medicine and started feeling different than you usually do, what, if anything, would you do*?"). The responses to this question were evaluated to determine if the adolescent subject would communicate a potential drug-related event to a parent, family member, doctor or pharmacist, or would stop use of the drug.

To address the third objective, the interviewer asked two additional open-ended questions about the meaning of the phrases in the behavior and mood-related warnings ("*What does the phrase 'unexpected changes in behavior, thoughts or mood' mean to you*?" and "*What does the phrase 'unexpected changes or problems when you sleep' mean to you*?").

Lastly, the REALM-Teen Test was administered to all adolescent subjects.

8.5.5 Primary Endpoint 1: Self-Selection

The first primary endpoint for this study was the number of subjects who had a correct overall response for the self-selection decision ("*Is this medicine Okay for you to use?")*, post mitigation. The target threshold was a lower limit of the two-sided 95% exact confidence interval for general population of adolescents with AR above 90%. FDA does not have guidelines for the conduct and analysis of self-selection or label comprehension studies for adolescents, so we chose to use the same thresholds we used for adults in this study.

Adolescent subjects achieved an overall correct self-selection score of 84.3% (lower bound of 80%).

8.5.6 Primary Endpoint 2: Action Subject Would Take to a Potential Drug-Related Effect

The second primary endpoint was designed to measure the number of subjects who correctly responded with a "safe-intended" action to a potential drug-related effect after taking Singulair Allergy. The protocol defined a "safe-intended" action as a response in which the adolescent subject would communicate a potential drug-related effect to a parent or family member, doctor or pharmacist or would stop use of the drug.

The target threshold for this end point was also the lower limit of the two-sided 95% exact confidence interval above 90% for the general population of adolescents with AR.

Overall, 96.6% (94.1% lower bound) of subjects provided a response that indicated a "safe-intended" action to a potential drug-related effect. Furthermore, among adolescents with incorrect self-selection, nearly all provided a response that indicated a safe-intended action (94.5% point estimate; n=52 of 55) to the question related to a potential drug-related effect.

8.5.7 Primary Endpoint 3: Interpretation of 2 Behavior- and Mood-Related Warnings.

The third primary endpoint was the number of subjects who correctly interpreted the meaning of the two behavior and mood-related event phrases on the Drug Facts label:

Stop use and ask a doctor if you

- "experience unexpected changes in behavior, thoughts or mood"
- "experience unexpected changes or problems when you sleep"

Primary endpoint 3 would meet the threshold if the lower limit of the two-sided 95% exact confidence interval for general population of adolescents with AR were above 90%.

The warning "unexpected changes in behavior, thoughts or mood" achieved an overall correct interpretation by 95.1% (92.3% lower bound), and "unexpected changes or problems when you sleep" achieved an overall correct interpretation by 95.7% (93.0% lower bound) of adolescents with AR.

8.5.8 Additional Analyses

Comorbidities

Additional analyses were conducted for two subgroups of subjects: adolescents with AR and comorbid depression, adolescents with AR and comorbid asthma. These groups were not augmented and were included to assess if any differences exist between general population subjects and those with these co-morbidities. These subgroup analyses showed that subjects were able to appropriately self-select Singulair Allergy at similar levels as the general population of adolescents as well as correctly interpret the behavior and mood-related warnings (achieving overall self-selection of 82%-83% and interpretation scores of 98%-100%).

Adolescents who have Low Literacy Skills

Additionally, 75.6% of adolescent subjects who had low literacy skills appropriately self-selected to not use Singulair Allergy. They achieved interpretation scores of 94.4% and 92.2% for the behavior and mood -related warnings.

Prior Rx Singulair Use

Adolescents who have previously used Rx Singulair for either asthma or allergies achieved self-selection scores ranging between 79.4%-84.9%, and achieved interpretation scores ranging from 90%-100% for both behavior and mood-related warnings.

Among Incorrect Self Selectors

Among the minority of incorrect self-selectors who chose to use Singulair Allergy against the age directive, 95%-96% understood the behavior and mood-related warnings and 95% (52 out of 55) understood how to react to a potential drug-related effect.

8.5.9 Summary

The results of this study demonstrated that 84% of adolescent subjects, 15-17 years old, could correctly self-select to not use Singulair Allergy. Subjects exhibited appropriate knowledge of what to do if potential drug-related effects were experienced and understood the two behavior and mood-related warnings on the Drug Facts label.

8.5.10 Overall OTC Development Program Summary

Taken together, the consumer studies for this Rx-to-OTC switch program show that the proposed Drug Facts label is well understood and provides consumers with the information necessary for the safe and appropriate use of Singulair Allergy in the OTC setting. Consumers, regardless of whether they had previously used Rx Singulair or not, or whether they suffered from asthma only or asthma with comorbid

AR, understood that the product is not intended to treat asthma and is only to be taken to treat AR. Further, behavior-related warnings were well understood by both adolescents (15-17 years old) and adults with AR. In addition, adolescents understood that the product is not intended for them.

The following table summarizes the three consumer study results.

Study/Objective	Results
SOLID: To establish that people with asthma (both with and without prior experience with Rx Singulair) understand that Singulair Allergy should not be used to treat asthma.	**% Correct Self-Selection** • With Prior Rx Singulair Experience: 91.7% (88.4% LB) • Without Prior Rx Singulair Experience: 96.3% (93.7% LB) • Subjects who have Low Literacy Skills: 90.8% (85.3% LB) **Label Comprehension of Primary Medical Risk Warnings** *"Do not use to treat asthma"* • With Prior Rx Singulair Experience: 91.7% (88.4% LB) • Without Prior Rx Singulair Experience: 92.3% (88.9% LB) • Subjects who have Low Literacy Skills: 79.1% (72.1 % LB) *"If you are currently taking asthma medications, do not stop taking them"* • With Prior Rx Singulair Experience: 94.0% (91.2% LB) • Without Prior Rx Singulair Experience: 96.0% (93.4% LB) • Subjects who have Low Literacy Skills: 87.7% (81.7 % LB) *"Children under 18 years of age, do not use"* • With Prior Rx Singulair Experience: 95.8% (93.3% LB) • Without Prior Rx Singulair Experience: 96.8% (94.4% LB) • Subjects who have Low Literacy Skills: 91.4% (86.0% LB)
Label Comprehension Warnings Study: To demonstrate that the behavior and mood-related warnings (BRAE) are well understood by adults with allergies.	**Label BRAE Warnings: % Correct Comprehension:** *"Stop use and ask a doctor if you experience unexpected changes in behavior, thoughts or mood"* • 97.5% (95.3% LB) *"Stop use and ask a doctor if you experience unexpected changes or problems when you sleep":* • 97.0% (94.4% LB)
Self-Selection and Warning Interpretation among Adolescents: To assess that 15-17 year olds understand that Singulair Allergy is intended only for adults and also to understand that these teens understand the behavior and mood-related warnings (BRAE).	**% Correct Self-Selection:** 84.3% (80.0% LB) **Safe-Intended Action:** 96.6% (94.1% LB) **BRAE Warnings:** % Correct Interpretation**:** 95.1-95.7% (92.3-93.0% LB)

BRAE = Behavior Related Adverse Event
LB = Lower Bound of the 95% Confidence Interval (CI)

9.0 BENEFIT AND RISK CONSIDERATIONS

Central to the decision regarding approval of any medication is a benefit-risk assessment. In the case of an Rx-to-OTC switch in which the product already has established efficacy and safety, this assessment evaluates the inherent benefits of increased access to an approved prescription medicine against the potential incremental risks that might come from a consumer using the medication without the involvement of an HCP.

Singulair Allergy will provide consumers an efficacious and well-tolerated new allergy treatment option in the OTC environment. Montelukast has a unique mechanism of action compared to the other OTC products used for treatment of AR. Singulair Allergy is an important alternative to available OTC therapies for the treatment of AR in adults 18 years of age and older because it offers the following benefits:

- proven efficacy;
- improved quality of life;
- favorable tolerability profile;
- absence of clinically-significant interaction with other medications;
- safe use with co-morbidities (e.g., diabetes or cardiovascular disease);
- can be used by OTC consumers who should not use a nasal decongestant;
- ease of administration regardless of food ingestion;
- non-sedating, once-daily dosing;
- no contraindications or need for dose adjustment in the elderly or adults with hepatic or renal impairment.

Singulair Allergy may help to improve, directly and indirectly, the social economic burden that AR has on the health care system in the U.S. by increasing consumer satisfaction with an additional OTC AR treatment option.

The low potential for serious medical consequences associated with incremental risk due to the greater access to this product are appropriate for an OTC product. When considering if Rx Singulair is an appropriate OTC candidate, it is important to consider the degree of incremental risk, above the current level of risk that already exists for this product in the prescription market. There are two important topics related to incremental risk considered to be relevant to this switch:

1. The potential for people with asthma to use this product off-label in an OTC setting to treat their asthma; and
2. The current Rx Singulair label contains several behavior and mood-related warnings that must be clearly communicated to an OTC consumer.

9.1 Benefit Assessment

The benefits of enhanced access to Singulair for allergy treatment include:

- Meeting consumers' need for additional treatment choices;
- Providing comprehensive symptom relief; and
- Offering favorable tolerability.

9.1.1 Consumer Need for Additional Treatment Choices

AR (AR) is the fifth most prevalent chronic disease in the U.S.[3] With nearly 75 million Americans having allergies, estimates place AR prevalence somewhere between 10 and 30 percent of all adults.[4,5]

Although not life threatening, AR is lifestyle-limiting and has a well-documented impact on health-related and overall quality of life measures. It affects school and work performance, sleep, and social life regardless of gender, age and social and ethnic background.[8] In fact, 40% of people with AR say their allergies have a moderate to significant impact on quality of life and 38% report an even greater impact, saying they "cannot tolerate" the discomfort from their allergies.[9] Additionally, more than 90% of patients with moderate to severe AR report that symptoms affect their ability to do daily activities and 80% report difficulty sleeping accompanied by increased fatigue during the day.[9,10] It has been documented that allergies account for nearly 10 million missed or lost workdays each year.[11]

According to a 2013 survey by the Consumer Healthcare Products Association, 90% of people with AR self-treat their symptoms regularly or occasionally.[14] In addition, nearly 60 percent only use OTC medicines or herbal/homeopathic products for their symptoms.[12] Therefore, OTC approval of products that treat a wide range of AR symptoms (e.g., daytime and nighttime nasal symptoms, including congestion, as well as non-nasal, including ocular symptoms) is critical for improving overall quality of life for a large population of people with allergies.

Although the symptoms of AR are readily recognizable and their impact on patient quality of life is significant, it has been reported that 35% of OTC allergy product users report switching among products with different antihistamines or combination ingredients and 75% report wanting more OTC allergy treatment choices.[31] This is not surprising considering that nearly 1 in 4 people with allergies is not fully satisfied with their current OTC choices.[32]

While there are currently a wide variety of OTC products available to treat allergy symptoms, each of these product classes also possess a certain degree of limitations as highlighted below:

- **Oral H_1-antihistamines**: First-generation antihistamines are characterized by poor receptor selectivity resulting in significant sedative and anticholinergic effects. Second-generation antihistamines have an improved adverse event profile versus the first generation but their use may be limited by drug-drug and/or drug-food interactions.[1,46]Antihistamines are not indicated to relieve nasal congestion.
- **Combination Oral Antihistamines/Decongestants:** Pseudoephedrine, a decongestant often combined with an antihistamine, is legally restricted to only be sold from locked cabinets or behind a counter. In addition, the OTC Drug Facts label for products containing pseudoephedrine cautions users to consult a doctor before use if they have liver or kidney disease, heart disease, high blood pressure, thyroid disease, diabetes or trouble urinating due to an enlarged prostate gland.[16,17]
- **Intranasal Cromolyn**: Intranasal cromolyn has modest efficacy and can be dosed 4-6 times daily. Also, it is recommended to initiate therapy one week in advance of anticipated contact with seasonal allergens.[19]
- **Intranasal Corticosteroids:** Triamcinalone acetonide is the newest entrant to the OTC allergy market. Nasal sprays are not the most preferred dosage form for the treatment of allergy and may be rejected by some people.[20] While an effective treatment for reducing inflammation of the nasal mucosa, it may take up to one week of daily use to feel the most symptom relief.

While these treatment choices exert their effect through a variety of actions, no other oral pill acts on CysLT receptors, the targeted mechanism of action of Singulair Allergy. Singulair Allergy would represent a new class of OTC allergy medicine, the first leukotriene inhibitor. The specific blockade of $CysLT_1$ receptors by montelukast is unique and the effect on peripheral blood eosinophil counts highlights its targeted mechanism of action on the inflammatory process, differentiating it from all other oral OTC agents used for the treatment of AR, particularly antihistamines. Singulair Allergy would offer other distinct benefits to consumers, such as the relief of nasal congestion in a single ingredient tablet, with few, if any, of the limitations present in the category today. The OTC approval of Singulair Allergy would provide people with AR an important new choice to treat their AR in the OTC market.

9.1.2 Comprehensive Symptom Relief

Singulair Allergy treats all of the major symptoms of AR: nasal congestion, often cited as the most bothersome and most severe allergy symptom; runny nose; itchy, watery eyes; sneezing; and itching of the nose. It would be the only single-ingredient, once daily OTC tablet that provides comprehensive symptom relief, including congestion.

9.1.3 Ease of Use by a Broad Population

Singulair Allergy is available as a tablet which is the most preferred consumer dosage form. It has a favorable tolerability profile, even at doses 90 times the 10 mg proposed OTC dose. In addition, it can be used concomitantly with a wide range of commonly prescribed and OTC drugs including thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants. In drug interaction studies, montelukast did not have clinically important effects on the pharmacokinetics of theophylline, prednisone, prednisolone, oral contraceptives, digoxin, and warfarin.

Further, in comparison to currently available OTC treatments for AR, montelukast can be used by a broad cross section of individuals, including geriatric populations, and those with, for example, hepatic or renal insufficiencies, cardiovascular disease, or glaucoma.

9.2 INCREMENTAL OTC RISK ASSESSMENT

Incremental risk describes the potential for unintended consequences resulting solely from OTC availability of a previously prescription-only product. These risks will result from consumer behavior in the absence of direct involvement with an HCP. When examining incremental risk, it is important to differentiate what new risks will be incurred by removing the HCP from the equation over risks that are inherent to the Rx product today. Examples of incremental risk include misdiagnosis of a condition, intentional abuse, intentional or accidental overdose/ingestion, intentional or unintentional off-label use with/without therapeutic intent, and worsened outcome due to self-management. Specifically, in the case of Singulair Allergy, evaluation of incremental risks should include analysis of possible off-label use by people with asthma and an analysis of consumers' ability to understand behavior and mood-related warnings without the involvement of an HCP.

9.2.1 Abuse and Overdose

Montelukast is non-addictive and has a very low potential for serious sequelae from accidental overdose. It has been administered at doses up to 200 mg/day to adult patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences. Acute overdose in post-marketing and clinical studies include reports in adults and children with a dose as high as 1000 mg. The most frequently occurring AEs were consistent with the safety profile of Rx Singulair 10 mg and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

9.2.2 Evaluation of Off-Label Use for Treatment of Asthma

Rx Singulair is indicated for the treatment of both AR and asthma, therefore, some people, particularly those who have used Rx Singulair, may recognize Singulair Allergy as the same medication that can be used to treat asthma. This raises the

question as to the potential for off-label use of OTC Singulair Allergy among individuals who may use the OTC product to treat their asthma.

As indicated in **Section 6.1**, this has been addressed through the labeling which is clearly indicated for AR and also includes several warnings related to asthma. This labeling which was tested in the OTC Development Program outlined in **Section 8.3** mitigates this potential risk.

For completeness, MCC conducted a theoretical analysis of the treatment behaviors of patients with asthma to ascertain what the potential incremental risk would be relative to the OTC approval of Singulair Allergy. The following sources were used in consideration of three scenarios explained below:

- National Heart, Lung and Blood Institute's National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3, 2007);
- Medical analysis by our internal MCC medical personnel;
- The opinions of key thought leaders in the field of asthma and allergy; and,
- Literature searches.

The first scenario considers the potential of a current Rx Singulair user purchasing the OTC product to treat their asthma resulting in this person potentially limiting contact with their current HCP. There is nothing in the literature to suggest that these patients will sever ties with their HCPs despite OTC access to a currently prescribed medication. Data suggest that up to 60% of patients with persistent asthma take at least two Rx medications at any given time,[33] which means that they rely on more than one medicine and also need to maintain their relationships with HCPs to obtain refills. Further, roughly 85% of patients with asthma report that they see their primary care physicians at least twice a year regardless of whether or not symptoms were controlled.[33] Therefore, while the replacement of Rx Singulair with OTC Singulair Allergy is not recommended to treat asthma, it is not likely to place patients with asthma at incremental risk as per the EPR3 Asthma Guidelines, nor should it impact current relationships with their HCPs. Furthermore, if a patient with asthma experiences a change in asthma control, it is expected that he or she would contact an HCP.

A second potential scenario involves the patients with asthma who use their prescribed asthma treatment intermittently but then choose to use OTC Singulair Allergy as sporadic therapy, either as a substitution or in addition to their prescribed medication. Related to substitution, data from the Improving Asthma Control Trial (IMPACT) [a double-blind, randomized trial that analyzed the efficacy of short-course corticosteroid treatment alone or in addition to daily inhaled corticosteroid (budesonide) or an oral leukotriene-receptor antagonist (zafirlukast)] demonstrate that some patients may benefit from symptom-driven intermittent treatment without increasing the risk for a higher frequency of asthma exacerbations.[34] Moreover, morning peak expiratory flow (PEF), as well as other objective measures of lung

function and airway biology [e.g. forced expiratory volume in one second (FEV_1), exhaled nitric oxide, sputum eosinophils] demonstrated equivalence among all treatments used intermittently.

Related to adding Singulair to their current therapy, data have shown that people with asthma (not achieving optimal control despite daily inhaled corticosteroids or long-acting $ß_2$-agonist therapy) who received add-on oral montelukast experience significant improvements in FEV_1/PEF ($p<0.0001$) as well as Asthma Control Test and the Mini-Asthma Quality of Life Questionnaire ($p<0.001$ for both, respectively).[35] This suggests that the incremental risk associated with add-on therapy, even if not prescribed, is minimal. These patients will either gain better symptom control or remain unchanged, and are unlikely to experience more exacerbations. These data are presented NOT to suggest that use of OTC Singulair in this way is in any way desirable but to provide clinical context for the likely sequelae if consumers override the label.

MCC has also considered a third scenario: patients who are currently being treated for asthma with product(s) other than Rx Singulair who choose to substitute their current prescribed treatment with OTC Singulair Allergy. Data suggest that up to 70% of patients taking inhaled corticosteroids (fluticasone propionate 100 µg bid) who switch to montelukast (5 mg or 10 mg at night) are able to maintain asthma control [as measured by FEV_1/PEF, use of rescue medication, hospitalization or utilization of urgent medical care, absence of febrile illness and an ACQ (Asthma Control Questionnaire) score <1.5] compared to up to 80% of patients who switch to fluticasone plus salmeterol (100 µg, 50 100 µg, respectively).[36] Moreover, the percentage of symptom-free days is similar among all substituted agents (78.7% to 85.8%). Notably, the rates of significant asthma exacerbations, again, an important measure of risk as stated by EPR3, did not differ significantly and remained relatively low. This suggests that deliberate substitution of prescribed asthma therapy with OTC Singulair Allergy, while not recommended, carries only a minor incremental risk and most importantly, the likelihood of an acute asthma exacerbation that might drive the patient to the emergency department or increase hospitalization remains low.

Finally, it is important to note that OTC Singulair Allergy will only be available in pill form and not as an inhaler, and there is no culture of use of oral medications to treat acute symptoms of asthma. To the contrary, there is decades-long history of use of rescue inhalers for rapid relief of acute symptoms. While absolute risk cannot be ruled out, it is unlikely that people with asthma will confuse OTC Singulair Allergy for their rescue medications.

It should also be noted that there is precedence for some drug categories to have the same active ingredient OTC and as an Rx for different indications and different populations. This occurs when some indications remain as a prescription due to the serious nature of the indication, or inability of consumers to accurately self-recognize, self-monitor and treat a condition. Examples include Proton Pump Inhibitors and H_2-antagonists which are acid reducers for several indications.

NSAIDs and topical antifungals are two other drug categories that have different indications and/or dosing OTC and Rx. These have been discussed previously in this briefing document.

In summary, appropriate measures have been taken on the Drug Facts label to prevent people with asthma from using this product in an OTC setting. The OTC Development Program clearly demonstrates that the proposed OTC label is well understood by people with asthma and the likelihood for this population to use Singulair Allergy is low. Further, while it is not recommended that people with asthma ever use OTC Singulair Allergy to treat their asthma, it is unlikely that, if it did occur, that this behavior will result in acute exacerbations or hospitalizations or undue incremental clinical risk as defined by EPR3 Asthma Guidelines.

9.2.3 Communication of Behavior or Mood-Related Warnings

The second topic to consider for incremental risk related to Singulair Allergy is the issue of behavior and mood-related changes which have been reported with Rx Singulair. MCC has carefully considered how to communicate to OTC consumers that they should “stop use and ask a doctor” if they experience behavior and mood-related changes.

For OTC Singulair Allergy, MCC has developed consumer language to communicate these important warnings to consumers in a clear and concise matter. The OTC label was developed to minimize any potential incremental risk of consumers using this product without the benefit of an HCP versus the risks already existing with the prescription product. Specifically, the following warnings are included on the OTC Drug Facts label:

Stop use and ask a doctor if

- You experience unexpected changes in behavior, thoughts or mood
- You experience unexpected changes or problems when you sleep

These two warnings were selected after qualitative testing of four label versions, during which it was determined that this language was the most effective to communicate broad categories of symptoms to consumers to convey the spectrum of potential neuropsychiatric events.

Two consumer studies demonstrated that 97% of adults with AR understood the warnings and 95% of adolescents could interpret the warnings appropriately. Additional details from these studies can be found in **Sections 8.4** and **8.5**, respectively.

Furthermore, MCC has proposed a CIL that will provide information about these warnings that is based on language from the Rx patient package insert that is currently provided to users of Rx Singulair today.

Given that these warnings are present on the OTC label, any potential incremental risk related to behavior and mood-related changes has been addressed with regard to use in the OTC environment.

10.0 CONCLUSION AND OVERALL RATIONALE SUPPORTING SINGULAIR ALLERGY

Expanding access to safe and effective OTC options with different mechanisms of action can help the millions of consumers who self-manage their AR. Montelukast has a mechanism of action different from any other agent approved and used for the treatment of AR.

- The clinical development program and the experience gained over the last 16 years have demonstrated that Singulair Allergy is effective and well-tolerated.
- Singulair Allergy will provide the benefits of a non-sedating, once-daily single-ingredient tablet available to treat all major allergy symptoms, including nasal congestion.
- It will provide an AR treatment option to OTC consumers who are not fully satisfied with current options, or who cannot use other OTC AR therapies because of adverse effects or underlying medical conditions.

The potential incremental risks associated with OTC availability of Singulair Allergy have been evaluated using a comprehensive review of clinical studies, post-marketing events, literature searches.

- MCC has addressed the potential for incremental risk through the development of OTC product labeling which has been validated through label comprehension and self-selection studies
- Study results demonstrate that the proposed Drug Facts label, which includes information about indication, warnings and appropriate age for use, was well-understood by consumers.
- The potential risks associated with increased access to Singulair Allergy are minimal and similar to those that currently exist with use of the prescription product.

Therefore, the benefits of broader access to Singulair, with its new mechanism of action, outweigh the risks. For all these reasons, Singulair Allergy is well-suited as an additional option for adults with AR who choose to self-manage their allergies with OTC medicines.

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APPENDICES

Appendix 1: Current Rx Singulair Labeling (Prescribing Information and Patient Package Insert)

Appendix 2: Individual Pivotal Study Data: Nasal and Eye Symptoms Scores and RQoL Questionnaire Data

Appendix 3: Patient Self-Rated Global Evaluation of AR (GEoAR)

Appendix 4: Summary of Analyses in Response to FDA Investigation of Behavior/Mood Changes Possibly Related to Leukotriene-Modifying Agents

Appendix 5: Consumer Research Studies Exclusion Criteria

Appendix 6: SOLID's Mitigation Plan

Appendix 1 Current Rx Singulair Labeling (Prescribing Information and Patient Package Insert)

Current Rx Singulair Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SINGULAIR safely and effectively. See full prescribing information for SINGULAIR.

SINGULAIR® (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules
Initial U.S. Approval: 1998

----------RECENT MAJOR CHANGES----------

Warnings and Precautions	
Neuropsychiatric Events (5.4)	03/2013
Eosinophilic Conditions (5.5)	06/2013

----------INDICATIONS AND USAGE----------

SINGULAIR is a leukotriene receptor antagonist indicated for:
- Prophylaxis and chronic treatment of asthma in patients 12 months of age and older (1.1).
- Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older (1.2).
- Relief of symptoms of allergic rhinitis (AR): seasonal allergic rhinitis (SAR) in patients 2 years of age and older, and perennial allergic rhinitis (PAR) in patients 6 months of age and older (1.3).

---------- DOSAGE AND ADMINISTRATION----------

Administration (by indications):
- Asthma (2.1): Once daily in the evening for patients 12 months and older.
- Acute prevention of EIB (2.2): One tablet at least 2 hours before exercise for patients 6 years of age and older.
- Seasonal allergic rhinitis (2.3): Once daily for patients 2 years and older.
- Perennial allergic rhinitis (2.3): Once daily for patients 6 months and older.

Dosage (by age) (2):
- 15 years and older: one 10-mg tablet.
- 6 to 14 years: one 5-mg chewable tablet.
- 2 to 5 years: one 4-mg chewable tablet or one packet of 4-mg oral granules.
- 6 to 23 months: one packet of 4-mg oral granules.

Patients with both asthma and allergic rhinitis should take only one dose daily in the evening (2.4). For oral granules: Must administer within 15 minutes after opening the packet (with or without mixing with food) (2.5).

---------- DOSAGE FORMS AND STRENGTHS ----------
- SINGULAIR 10-mg Film-Coated Tablets
- SINGULAIR 5-mg and 4-mg Chewable Tablets
- SINGULAIR 4-mg Oral Granules (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to any component of this product (4).

----------WARNINGS AND PRECAUTIONS----------
- Do not prescribe SINGULAIR to treat an acute asthma attack (5.1).
- Advise patients to have appropriate rescue medication available (5.1).
- Inhaled corticosteroid may be reduced gradually. Do not abruptly substitute SINGULAIR for inhaled or oral corticosteroids (5.2).
- Patients with known aspirin sensitivity should continue to avoid aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR (5.3).
- Neuropsychiatric events have been reported with SINGULAIR. Instruct patients to be alert for neuropsychiatric events. Evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur (5.4 and 6.2).
- Systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, has been reported. These events have been sometimes associated with the reduction of oral corticosteroid therapy (5.5 and 6.2).
- Inform patients with phenylketonuria that the 4-mg and 5-mg chewable tablets contain phenylalanine (5.6).

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥5% and greater than placebo listed in descending order of frequency): upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

MSD

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Asthma

SINGULAIR® is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

1.2 Exercise-Induced Bronchoconstriction (EIB)

SINGULAIR is indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older.

1.3 Allergic Rhinitis

SINGULAIR is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Asthma

SINGULAIR should be taken once daily in the evening. The following doses are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one packet of 4-mg oral granules.

For pediatric patients 12 to 23 months of age: one packet of 4-mg oral granules.

Safety and effectiveness in pediatric patients less than 12 months of age with asthma have not been established.

There have been no clinical trials in patients with asthma to evaluate the relative efficacy of morning versus evening dosing. The pharmacokinetics of montelukast are similar whether dosed in the morning or evening. Efficacy has been demonstrated for asthma when montelukast was administered in the evening without regard to time of food ingestion.

2.2 Exercise-Induced Bronchoconstriction (EIB)

For prevention of EIB, a single dose of SINGULAIR should be taken at least 2 hours before exercise. The following doses are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

An additional dose of SINGULAIR should not be taken within 24 hours of a previous dose. Patients already taking SINGULAIR daily for another indication (including chronic asthma) should not take an additional dose to prevent EIB. All patients should have available for rescue a short-acting β-agonist. Safety and efficacy in patients younger than 6 years of age have not been established. Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

2.3 Allergic Rhinitis

For allergic rhinitis, SINGULAIR should be taken once daily. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening without regard to time of food ingestion. The time of administration may be individualized to suit patient needs.

The following doses for the treatment of symptoms of seasonal allergic rhinitis are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one packet of 4-mg oral granules.

Safety and effectiveness in pediatric patients younger than 2 years of age with seasonal allergic rhinitis have not been established.

The following doses for the treatment of symptoms of perennial allergic rhinitis are recommended:

For adults and adolescents 15 years of age and older: one 10-mg tablet.

For pediatric patients 6 to 14 years of age: one 5-mg chewable tablet.

For pediatric patients 2 to 5 years of age: one 4-mg chewable tablet or one packet of 4-mg oral granules.

For pediatric patients 6 to 23 months of age: one packet of 4-mg oral granules.

Safety and effectiveness in pediatric patients younger than 6 months of age with perennial allergic rhinitis have not been established.

2.4 Asthma and Allergic Rhinitis

Patients with both asthma and allergic rhinitis should take only one SINGULAIR dose daily in the evening.

2.5 Instructions for Administration of Oral Granules

SINGULAIR 4-mg oral granules can be administered either directly in the mouth, dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk, or mixed with a spoonful of cold or room temperature soft foods; based on stability studies, only applesauce, carrots, rice, or ice cream should be used. The packet should not be opened until ready to use. After opening the packet, the full dose (with or without mixing with baby formula, breast milk, or food) must be administered within 15 minutes. If mixed with baby formula, breast milk, or food, SINGULAIR oral granules must not be stored for future use. Discard any unused portion. SINGULAIR oral granules are not intended to be dissolved in any liquid other than baby formula or breast milk for administration. However, liquids may be taken subsequent to administration. SINGULAIR oral granules can be administered without regard to the time of meals.

3 DOSAGE FORMS AND STRENGTHS

- SINGULAIR 10-mg Film-Coated Tablets are beige, rounded square-shaped tablets, with code MRK 117 or MSD 117 on one side and SINGULAIR on the other.
- SINGULAIR 5-mg Chewable Tablets are pink, round, bi-convex-shaped tablets, with code MRK 275 or MSD 275 on one side and SINGULAIR on the other.
- SINGULAIR 4-mg Chewable Tablets are pink, oval, bi-convex-shaped tablets, with code MRK 711 or MSD 711 on one side and SINGULAIR on the other.
- SINGULAIR 4-mg Oral Granules are white granules with 500 mg net weight, packed in a child-resistant foil packet.

4 CONTRAINDICATIONS

- Hypersensitivity to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Asthma

SINGULAIR is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Patients should be advised to have appropriate rescue medication available. Therapy with SINGULAIR can be continued during acute exacerbations of asthma. Patients who have exacerbations of asthma after exercise should have available for rescue a short-acting inhaled β-agonist.

5.2 Concomitant Corticosteroid Use

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR should not be abruptly substituted for inhaled or oral corticosteroids.

5.3 Aspirin Sensitivity

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR. Although SINGULAIR is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients *[see Clinical Studies (14.1)]*.

5.4 Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking

and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur *[see Adverse Reactions (6.2)].*

5.5 Eosinophilic Conditions

Patients with asthma on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events have been sometimes associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established *[see Adverse Reactions (6.2)].*

5.6 Phenylketonuria

Phenylketonuric patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842 mg per 4-mg and 5-mg chewable tablet, respectively.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In the following description of clinical trials experience, adverse reactions are listed regardless of causality assessment.

The most common adverse reactions (incidence ≥5% and greater than placebo; listed in descending order of frequency) in controlled clinical trials were: upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis.

Adults and Adolescents 15 Years of Age and Older with Asthma

SINGULAIR has been evaluated for safety in approximately 2950 adult and adolescent patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse experiences reported with SINGULAIR occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo:

Table 1: Adverse Experiences Occurring in ≥1% of Patients with an Incidence Greater than that in Patients Treated with Placebo

	SINGULAIR 10 mg/day (%) (n=1955)	Placebo (%) (n=1180)
Body As A Whole		
Pain, abdominal	2.9	2.5
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Trauma	1.0	0.8
Digestive System Disorders		
Dyspepsia	2.1	1.1
Pain, dental	1.7	1.0
Gastroenteritis, infectious	1.5	0.5
Nervous System/Psychiatric		
Headache	18.4	18.1
Dizziness	1.9	1.4
Respiratory System Disorders		
Influenza	4.2	3.9
Cough	2.7	2.4
Congestion, nasal	1.6	1.3
Skin/Skin Appendages Disorder		
Rash	1.6	1.2
*Laboratory Adverse Experiences**		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

* Number of patients tested (SINGULAIR and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.

The frequency of less common adverse events was comparable between SINGULAIR and placebo.

The safety profile of SINGULAIR, when administered as a single dose for prevention of EIB in adult and adolescent patients 15 years of age and older, was consistent with the safety profile previously described for SINGULAIR.

Cumulatively, 569 patients were treated with SINGULAIR for at least 6 months, 480 for one year, and 49 for two years in clinical trials. With prolonged treatment, the adverse experience profile did not significantly change.

Pediatric Patients 6 to 14 Years of Age with Asthma

SINGULAIR has been evaluated for safety in 476 pediatric patients 6 to 14 years of age. Cumulatively, 289 pediatric patients were treated with SINGULAIR for at least 6 months, and 241 for one year or longer in clinical trials. The safety profile of SINGULAIR in the 8-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6 to 14 years of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and laryngitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

The safety profile of SINGULAIR, when administered as a single dose for prevention of EIB in pediatric patients 6 years of age and older, was consistent with the safety profile previously described for SINGULAIR.

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for SINGULAIR. In a 56-week, double-blind study evaluating growth rate in pediatric patients 6 to 8 years of age receiving SINGULAIR, the following events not previously observed with the use of SINGULAIR in this age group occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: headache, rhinitis (infective), varicella, gastroenteritis, atopic dermatitis, acute bronchitis, tooth infection, skin infection, and myopia.

Pediatric Patients 2 to 5 Years of Age with Asthma

SINGULAIR has been evaluated for safety in 573 pediatric patients 2 to 5 years of age in single- and multiple-dose studies. Cumulatively, 426 pediatric patients 2 to 5 years of age were treated with SINGULAIR for at least 3 months, 230 for 6 months or longer, and 63 patients for one year or longer in clinical trials. In pediatric patients 2 to 5 years of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis.

Pediatric Patients 6 to 23 Months of Age with Asthma

Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established.

SINGULAIR has been evaluated for safety in 175 pediatric patients 6 to 23 months of age. The safety profile of SINGULAIR in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatric patients 2 to 14 years of age. In pediatric patients 6 to 23 months of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo.

Adults and Adolescents 15 Years of Age and Older with Seasonal Allergic Rhinitis

SINGULAIR has been evaluated for safety in 2199 adult and adolescent patients 15 years of age and older in clinical trials. SINGULAIR administered once daily in the morning or in the evening had a safety profile similar to that of placebo. In placebo-controlled clinical trials, the following event was reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo: upper respiratory infection, 1.9% of patients receiving SINGULAIR vs. 1.5% of patients receiving placebo. In a 4-week, placebo-controlled clinical study, the safety profile was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

Pediatric Patients 2 to 14 Years of Age with Seasonal Allergic Rhinitis

SINGULAIR has been evaluated in 280 pediatric patients 2 to 14 years of age in a 2-week, multicenter, double-blind, placebo-controlled, parallel-group safety study. SINGULAIR administered once daily in the evening had a safety profile similar to that of placebo. In this study, the following events occurred with a frequency ≥2% and at an incidence greater than placebo: headache, otitis media, pharyngitis, and upper respiratory infection.

Adults and Adolescents 15 Years of Age and Older with Perennial Allergic Rhinitis

SINGULAIR has been evaluated for safety in 3357 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis of whom 1632 received SINGULAIR in two, 6-week, clinical studies. SINGULAIR administered once daily had a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following events were reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo.

Pediatric Patients 6 Months to 14 Years of Age with Perennial Allergic Rhinitis

The safety in patients 2 to 14 years of age with perennial allergic rhinitis is supported by the safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 6 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of SINGULAIR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: increased bleeding tendency, thrombocytopenia.

Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.

Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor *[see Warnings and Precautions (5.4)]*.

Nervous system disorders: drowsiness, paraesthesia/hypoesthesia, seizures.

Cardiac disorders: palpitations.

Respiratory, thoracic and mediastinal disorders: epistaxis, pulmonary eosinophilia.

Gastrointestinal disorders: diarrhea, dyspepsia, nausea, pancreatitis, vomiting.

Hepatobiliary disorders: Cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with SINGULAIR. Most of these occurred in combination with other confounding factors, such as use of other medications, or when SINGULAIR was administered to patients who had underlying potential for liver disease such as alcohol use or other forms of hepatitis.

Skin and subcutaneous tissue disorders: angioedema, bruising, erythema multiforme, erythema nodosum, pruritus, Stevens-Johnson syndrome/toxic epidermal necrolysis, urticaria.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.

General disorders and administration site conditions: edema.

Patients with asthma on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events have been sometimes associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients *[see Warnings and Precautions (5.5)].*

7 DRUG INTERACTIONS

No dose adjustment is needed when SINGULAIR is co-administered with theophylline, prednisone, prednisolone, oral contraceptives, terfenadine, digoxin, warfarin, gemfibrozil, itraconazole, thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, decongestants, and Cytochrome P450 (CYP) enzyme inducers *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Teratogenic Effect: No teratogenicity was observed in rats and rabbits at doses approximately 100 and 110 times, respectively, the maximum recommended daily oral dose in adults based on AUCs *[see Nonclinical Toxicology (13.2)].*

During worldwide marketing experience, congenital limb defects have been rarely reported in the offspring of women being treated with SINGULAIR during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and SINGULAIR has not been established.

8.3 Nursing Mothers

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

8.4 Pediatric Use

Safety and efficacy of SINGULAIR have been established in adequate and well-controlled studies in pediatric patients with asthma 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults *[see Adverse Reactions (6.1), Clinical Pharmacology, Special Populations (12.3), and Clinical Studies (14.1, 14.2)].*

The efficacy of SINGULAIR for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age and for the treatment of perennial allergic rhinitis in pediatric patients 6 months to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

The safety of SINGULAIR 4-mg chewable tablets in pediatric patients 2 to 5 years of age with asthma has been demonstrated by adequate and well-controlled data *[see Adverse Reactions (6.1)].* Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma and is based on similar pharmacokinetic data, as well as the assumption that the

disease course, pathophysiology and the drug's effect are substantially similar among these populations. Efficacy in this age group is supported by exploratory efficacy assessments from a large, well-controlled safety study conducted in patients 2 to 5 years of age.

The safety of SINGULAIR 4-mg oral granules in pediatric patients 12 to 23 months of age with asthma has been demonstrated in an analysis of 172 pediatric patients, 124 of whom were treated with SINGULAIR, in a 6-week, double-blind, placebo-controlled study *[see Adverse Reactions (6.1)].* Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma based on similar mean systemic exposure (AUC), and that the disease course, pathophysiology and the drug's effect are substantially similar among these populations, supported by efficacy data from a safety trial in which efficacy was an exploratory assessment.

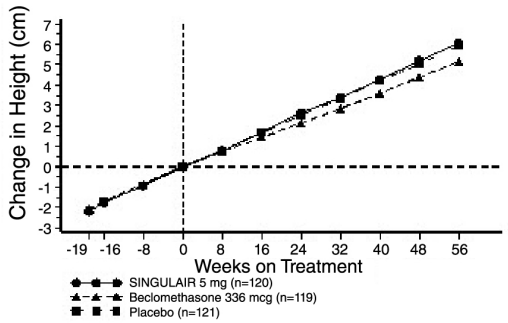
The safety of SINGULAIR 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile *[see Adverse Reactions (6.1)].* The safety of SINGULAIR 4-mg oral granules in pediatric patients as young as 6 months of age with perennial allergic rhinitis is supported by extrapolation from safety data obtained from studies conducted in pediatric patients 6 months to 23 months of age with asthma and from pharmacokinetic data comparing systemic exposures in patients 6 months to 23 months of age to systemic exposures in adults.

The safety and effectiveness in pediatric patients below the age of 12 months with asthma, 6 months with perennial allergic rhinitis, and 6 years with exercise-induced bronchoconstriction have not been established.

Growth Rate in Pediatric Patients

A 56-week, multi-center, double-blind, randomized, active- and placebo-controlled parallel group study was conducted to assess the effect of SINGULAIR on growth rate in 360 patients with mild asthma, aged 6 to 8 years. Treatment groups included SINGULAIR 5 mg once daily, placebo, and beclomethasone dipropionate administered as 168 mcg twice daily with a spacer device. For each subject, a growth rate was defined as the slope of a linear regression line fit to the height measurements over 56 weeks. The primary comparison was the difference in growth rates between SINGULAIR and placebo groups. Growth rates, expressed as least-squares (LS) mean (95% CI) in cm/year, for the SINGULAIR, placebo, and beclomethasone treatment groups were 5.67 (5.46, 5.88), 5.64 (5.42, 5.86), and 4.86 (4.64, 5.08), respectively. The differences in growth rates, expressed as least-squares (LS) mean (95% CI) in cm/year, for SINGULAIR minus placebo, beclomethasone minus placebo, and SINGULAIR minus beclomethasone treatment groups were 0.03 (-0.26, 0.31), -0.78 (-1.06, -0.49); and 0.81 (0.53, 1.09), respectively. Growth rate (expressed as mean change in height over time) for each treatment group is shown in FIGURE 1.

Figure 1: Change in Height (cm) from Randomization Visit by Scheduled Week (Treatment Group Mean ± Standard Error* of the Mean)



*The standard errors of the treatment group means in change in height are too small to be visible on the plot

8.5 Geriatric Use

Of the total number of subjects in clinical studies of montelukast, 3.5% were 65 years of age and over, and 0.4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older

individuals cannot be ruled out. The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

8.6 Hepatic Insufficiency

No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Insufficiency

No dosage adjustment is recommended in patients with renal insufficiency *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

There have been reports of acute overdosage in post-marketing experience and clinical studies with SINGULAIR. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of overdosage reports. The most frequently occurring adverse experiences were consistent with the safety profile of SINGULAIR and included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor hyperactivity.

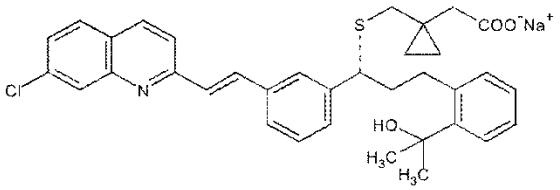
It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

11 DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

Montelukast sodium is described chemically as [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.

The empirical formula is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18. The structural formula is:



Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Each 10-mg film-coated SINGULAIR tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg of montelukast, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Each 4-mg and 5-mg chewable SINGULAIR tablet contains 4.2 and 5.2 mg montelukast sodium, respectively, which are equivalent to 4 and 5 mg of montelukast, respectively. Both chewable tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Each packet of SINGULAIR 4-mg oral granules contains 4.2 mg montelukast sodium, which is equivalent to 4 mg of montelukast. The oral granule formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis.

Montelukast is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

12.2 Pharmacodynamics

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD_4-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12), SINGULAIR inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

The effect of SINGULAIR on eosinophils in the peripheral blood was examined in clinical trials. In patients with asthma aged 2 years and older who received SINGULAIR, a decrease in mean peripheral blood eosinophil counts ranging from 9% to 15% was noted, compared with placebo, over the double-blind treatment periods. In patients with seasonal allergic rhinitis aged 15 years and older who received SINGULAIR, a mean increase of 0.2% in peripheral blood eosinophil counts was noted, compared with a mean increase of 12.5% in placebo-treated patients, over the double-blind treatment periods; this reflects a mean difference of 12.3% in favor of SINGULAIR. The relationship between these observations and the clinical benefits of montelukast noted in the clinical trials is not known *[see Clinical Studies (14)].*

12.3 Pharmacokinetics

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean C_{max} is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean C_{max} is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

The 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state. The co-administration of the oral granule formulation with applesauce did not have a clinically significant effect on the pharmacokinetics of montelukast. A high fat meal in the morning did not affect the AUC of montelukast oral granules; however, the meal decreased C_{max} by 35% and prolonged T_{max} from 2.3 ± 1.0 hours to 6.4 ± 2.9 hours.

The safety and efficacy of SINGULAIR in patients with asthma were demonstrated in clinical trials in which the 10-mg film-coated tablet and 5-mg chewable tablet formulations were administered in the evening without regard to the time of food ingestion. The safety of SINGULAIR in patients with asthma was also demonstrated in clinical trials in which the 4-mg chewable tablet and 4-mg oral granule formulations were administered in the evening without regard to the time of food ingestion. The safety and efficacy of SINGULAIR in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10-mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

The comparative pharmacokinetics of montelukast when administered as two 5-mg chewable tablets versus one 10-mg film-coated tablet have not been evaluated.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Metabolism

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

In vitro studies using human liver microsomes indicate that CYP3A4, 2C8, and 2C9 are involved in the metabolism of montelukast. At clinically relevant concentrations, 2C8 appears to play a major role in the metabolism of montelukast.

Elimination

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Populations

Hepatic Insufficiency: Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast AUC following a single 10-mg dose. The elimination of montelukast was slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of SINGULAIR in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

Renal Insufficiency: Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Gender: The pharmacokinetics of montelukast are similar in males and females.

Race: Pharmacokinetic differences due to race have not been studied.

Adolescents and Pediatric Patients: Pharmacokinetic studies evaluated the systemic exposure of the 4-mg oral granule formulation in pediatric patients 6 to 23 months of age, the 4-mg chewable tablets in pediatric patients 2 to 5 years of age, the 5-mg chewable tablets in pediatric patients 6 to 14 years of age, and the 10-mg film-coated tablets in young adults and adolescents ≥15 years of age.

The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents ≥15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years of age.

The mean systemic exposure of the 4-mg chewable tablet in pediatric patients 2 to 5 years of age and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age is similar to the mean systemic exposure of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2 to 5 years of age.

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Based on population analyses, the mean AUC (4296 ng•hr/mL [range 1200 to 7153]) was 60% higher and the mean C_{max} (667 ng/mL [range 201 to 1058]) was 89% higher than those observed in adults (mean AUC 2689 ng•hr/mL [range 1521 to 4595]) and mean C_{max} (353 ng/mL [range 180 to 548]). The systemic exposure in children 12 to 23 months of age was less variable, but was still higher than that observed in adults. The mean AUC (3574 ng•hr/mL [range 2229 to 5408]) was 33% higher and the mean C_{max} (562 ng/mL [range 296 to 814]) was 60% higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in 26 children 6 to 23 months of age were similar to that of patients two years and above *[see Adverse Reactions (6.1)]*. The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age for the treatment of asthma, or for pediatric patients 6 to 23 months of age for the treatment of perennial allergic rhinitis. Since the 4-mg oral granule formulation is bioequivalent to the 4-mg

chewable tablet, it can also be used as an alternative formulation to the 4-mg chewable tablet in pediatric patients 2 to 5 years of age.

Drug-Drug Interactions

Theophylline, Prednisone, and Prednisolone: SINGULAIR has been administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, and prednisolone.

Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state, did not cause clinically significant changes in the kinetics of a single intravenous dose of theophylline [predominantly a cytochrome P450 (CYP) 1A2 substrate]. Montelukast at doses of ≥100 mg daily dosed to pharmacokinetic steady state, did not cause any clinically significant change in plasma profiles of prednisone or prednisolone following administration of either oral prednisone or intravenous prednisolone.

Oral Contraceptives, Terfenadine, Digoxin, and Warfarin: In drug interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin. Montelukast at doses of ≥100 mg daily dosed to pharmacokinetic steady state did not significantly alter the plasma concentrations of either component of an oral contraceptive containing norethindrone 1 mg/ethinyl estradiol 35 mcg. Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state did not change the plasma concentration profile of terfenadine (a substrate of CYP3A4) or fexofenadine, the carboxylated metabolite, and did not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily; did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin; did not change the pharmacokinetic profile of warfarin (primarily a substrate of CYP2C9, 3A4 and 1A2) or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the International Normalized Ratio (INR).

Thyroid Hormones, Sedative Hypnotics, Non-Steroidal Anti-Inflammatory Agents, Benzodiazepines, and Decongestants: Although additional specific interaction studies were not performed, SINGULAIR was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Cytochrome P450 (CYP) Enzyme Inducers: Phenobarbital, which induces hepatic metabolism, decreased the area under the plasma concentration curve (AUC) of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent CYP enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

Effect of Montelukast on Cytochrome P450 (CYP) Enzymes: Montelukast is a potent inhibitor of CYP2C8 *in vitro.* However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) in 12 healthy individuals demonstrated that the pharmacokinetics of rosiglitazone are not altered when the drugs are coadministered, indicating that montelukast does not inhibit CYP2C8 *in vivo*. Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide). Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit CYP 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Cytochrome P450 (CYP) Enzyme Inhibitors: In vitro studies have shown that montelukast is a substrate of CYP 2C8, 2C9, and 3A4. Co-administration of montelukast with itraconazole, a strong CYP 3A4 inhibitor, resulted in no significant increase in the systemic exposure of montelukast. Data from a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) demonstrated that gemfibrozil, at a therapeutic dose, increased the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, gemfibrozil, and montelukast did not further increase the systemic exposure of montelukast. Based on available clinical experience, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil *[see Overdosage (10)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was seen in carcinogenicity studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. The estimated exposure in rats was approximately 120 and 75 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose. The estimated exposure in mice was approximately 45 and 25 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose.

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

No teratogenicity was observed at oral doses up to 400 mg/kg/day and 300 mg/kg/day in rats and rabbits, respectively. These doses were approximately 100 and 110 times the maximum recommended daily oral dose in adults, respectively, based on AUCs. Montelukast crosses the placenta following oral dosing in rats and rabbits *[see Pregnancy (8.1)]*.

14 CLINICAL STUDIES

14.1 Asthma

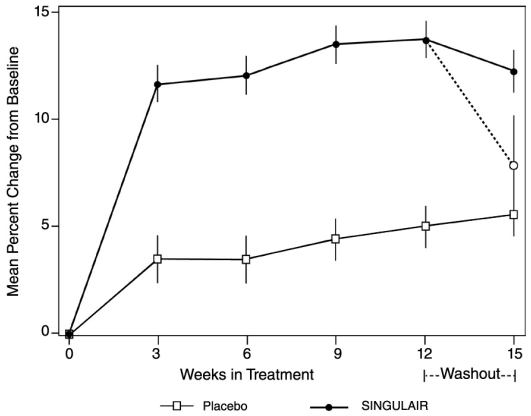
Adults and Adolescents 15 Years of Age and Older with Asthma

Clinical trials in adults and adolescents 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily.

The efficacy of SINGULAIR for the chronic treatment of asthma in adults and adolescents 15 years of age and older was demonstrated in two (U.S. and Multinational) similarly designed, randomized, 12-week, double-blind, placebo-controlled trials in 1576 patients (795 treated with SINGULAIR, 530 treated with placebo, and 251 treated with active control). The median age was 33 years (range 15 to 85); 56.8% were females and 43.2% were males. The ethnic/racial distribution in these studies was 71.6% Caucasian, 17.7% Hispanic, 7.2% other origins and 3.5% Black. Patients had mild or moderate asthma and were non-smokers who required approximately 5 puffs of inhaled β-agonist per day on an "as-needed" basis. The patients had a mean baseline percent of predicted forced expiratory volume in 1 second (FEV_1) of 66% (approximate range, 40 to 90%). The co-primary endpoints in these trials were FEV_1 and daytime asthma symptoms. In both studies after 12 weeks, a random subset of patients receiving SINGULAIR was switched to placebo for an additional 3 weeks of double-blind treatment to evaluate for possible rebound effects.

The results of the U.S. trial on the primary endpoint, morning FEV_1, expressed as mean percent change from baseline averaged over the 12-week treatment period, are shown in FIGURE 2. Compared with placebo, treatment with one SINGULAIR 10-mg tablet daily in the evening resulted in a statistically significant increase in FEV_1 percent change from baseline (13.0%-change in the group treated with SINGULAIR vs. 4.2%-change in the placebo group, $p<0.001$); the change from baseline in FEV_1 for SINGULAIR was 0.32 liters compared with 0.10 liters for placebo, corresponding to a between-group difference of 0.22 liters ($p<0.001$, 95% CI 0.17 liters, 0.27 liters). The results of the Multinational trial on FEV_1 were similar.

Figure 2: FEV_1 Mean Percent Change from Baseline
(U.S. Trial: SINGULAIR N=406; Placebo N=270)
(ANOVA Model)



The effect of SINGULAIR on other primary and secondary endpoints, represented by the Multinational study is shown in TABLE 2. Results on these endpoints were similar in the US study.

Table 2: Effect of SINGULAIR on Primary and Secondary Endpoints in a Multinational Placebo-controlled Trial (ANOVA Model)

	SINGULAIR			Placebo		
Endpoint	N	Baseline	Mean Change from Baseline	N	Baseline	Mean Change from Baseline
Daytime Asthma Symptoms (0 to 6 scale)	372	2.35	-0.49*	245	2.40	-0.26
β-agonist (puffs per day)	371	5.35	-1.65*	241	5.78	-0.42
AM PEFR (L/min)	372	339.57	25.03*	244	335.24	1.83
PM PEFR (L/min)	372	355.23	20.13*	244	354.02	-0.49
Nocturnal Awakenings (#/week)	285	5.46	-2.03*	195	5.57	-0.78

* $p<0.001$, compared with placebo

Both studies evaluated the effect of SINGULAIR on secondary outcomes, including asthma attack (utilization of health-care resources such as an unscheduled visit to a doctor's office, emergency room, or hospital; or treatment with oral, intravenous, or intramuscular corticosteroid), and use of oral corticosteroids for asthma rescue. In the Multinational study, significantly fewer patients (15.6% of patients) on SINGULAIR experienced asthma attacks compared with patients on placebo (27.3%, $p<0.001$). In the US study, 7.8% of patients on SINGULAIR and 10.3% of patients on placebo experienced asthma attacks, but the difference between the two treatment groups was not significant ($p=0.334$). In the Multinational study, significantly fewer patients (14.8% of patients) on SINGULAIR were prescribed oral corticosteroids for asthma rescue compared with patients on placebo (25.7%, $p<0.001$). In the US study, 6.9% of patients on SINGULAIR and 9.9% of patients on placebo were prescribed oral corticosteroids for asthma rescue, but the difference between the two treatment groups was not significant ($p=0.196$).

Onset of Action and Maintenance of Effects

In each placebo-controlled trial in adults, the treatment effect of SINGULAIR, measured by daily diary card parameters, including symptom scores, "as-needed" β-agonist use, and PEFR measurements, was achieved after the first dose and was maintained throughout the dosing interval (24 hours). No significant change in treatment effect was observed during continuous once-daily evening administration in non-placebo-controlled extension trials for up to one year. Withdrawal of SINGULAIR in asthmatic patients after 12 weeks of continuous use did not cause rebound worsening of asthma.

Pediatric Patients 6 to 14 Years of Age with Asthma

The efficacy of SINGULAIR in pediatric patients 6 to 14 years of age was demonstrated in one 8-week, double-blind, placebo-controlled trial in 336 patients (201 treated with SINGULAIR and 135 treated with placebo) using an inhaled β-agonist on an "as-needed" basis. The patients had a mean baseline percent predicted FEV_1 of 72% (approximate range, 45 to 90%) and a mean daily inhaled β-agonist requirement of 3.4 puffs of albuterol. Approximately 36% of the patients were on inhaled corticosteroids. The median age

was 11 years (range 6 to 15); 35.4% were females and 64.6% were males. The ethnic/racial distribution in this study was 80.1% Caucasian, 12.8% Black, 4.5% Hispanic, and 2.7% other origins.

Compared with placebo, treatment with one 5-mg SINGULAIR chewable tablet daily resulted in a significant improvement in mean morning FEV_1 percent change from baseline (8.7% in the group treated with SINGULAIR vs. 4.2% change from baseline in the placebo group, $p<0.001$). There was a significant decrease in the mean percentage change in daily "as-needed" inhaled β-agonist use (11.7% decrease from baseline in the group treated with SINGULAIR vs. 8.2% increase from baseline in the placebo group, $p<0.05$). This effect represents a mean decrease from baseline of 0.56 and 0.23 puffs per day for the montelukast and placebo groups, respectively. Subgroup analyses indicated that younger pediatric patients aged 6 to 11 had efficacy results comparable to those of the older pediatric patients aged 12 to 14.

Similar to the adult studies, no significant change in the treatment effect was observed during continuous once-daily administration in one open-label extension trial without a concurrent placebo group for up to 6 months.

Pediatric Patients 2 to 5 Years of Age with Asthma

The efficacy of SINGULAIR for the chronic treatment of asthma in pediatric patients 2 to 5 years of age was explored in a 12-week, placebo-controlled safety and tolerability study in 689 patients, 461 of whom were treated with SINGULAIR. The median age was 4 years (range 2 to 6); 41.5% were females and 58.5% were males. The ethnic/racial distribution in this study was 56.5% Caucasian, 20.9% Hispanic, 14.4% other origins, and 8.3% Black.

While the primary objective was to determine the safety and tolerability of SINGULAIR in this age group, the study included exploratory efficacy evaluations, including daytime and overnight asthma symptom scores, β-agonist use, oral corticosteroid rescue, and the physician's global evaluation. The findings of these exploratory efficacy evaluations, along with pharmacokinetics and extrapolation of efficacy data from older patients, support the overall conclusion that SINGULAIR is efficacious in the maintenance treatment of asthma in patients 2 to 5 years of age.

Effects in Patients on Concomitant Inhaled Corticosteroids

Separate trials in adults evaluated the ability of SINGULAIR to add to the clinical effect of inhaled corticosteroids and to allow inhaled corticosteroid tapering when used concomitantly.

One randomized, placebo-controlled, parallel-group trial (n=226) enrolled adults with stable asthma with a mean FEV_1 of approximately 84% of predicted who were previously maintained on various inhaled corticosteroids (delivered by metered-dose aerosol or dry powder inhalers). The median age was 41.5 years (range 16 to 70); 52.2% were females and 47.8% were males. The ethnic/racial distribution in this study was 92.0% Caucasian, 3.5% Black, 2.2% Hispanic, and 2.2% Asian. The types of inhaled corticosteroids and their mean baseline requirements included beclomethasone dipropionate (mean dose, 1203 mcg/day), triamcinolone acetonide (mean dose, 2004 mcg/day), flunisolide (mean dose, 1971 mcg/day), fluticasone propionate (mean dose, 1083 mcg/day), or budesonide (mean dose, 1192 mcg/day). Some of these inhaled corticosteroids were non-U.S.-approved formulations, and doses expressed may not be ex-actuator. The pre-study inhaled corticosteroid requirements were reduced by approximately 37% during a 5- to 7-week placebo run-in period designed to titrate patients toward their lowest effective inhaled corticosteroid dose. Treatment with SINGULAIR resulted in a further 47% reduction in mean inhaled corticosteroid dose compared with a mean reduction of 30% in the placebo group over the 12-week active treatment period ($p\leq0.05$). It is not known whether the results of this study can be generalized to patients with asthma who require higher doses of inhaled corticosteroids or systemic corticosteroids.

In another randomized, placebo-controlled, parallel-group trial (n=642) in a similar population of adult patients previously maintained, but not adequately controlled, on inhaled corticosteroids (beclomethasone 336 mcg/day), the addition of SINGULAIR to beclomethasone resulted in statistically significant improvements in FEV_1 compared with those patients who were continued on beclomethasone alone or those patients who were withdrawn from beclomethasone and treated with montelukast or placebo alone over the last 10 weeks of the 16-week, blinded treatment period. Patients who were randomized to treatment arms containing beclomethasone had statistically significantly better asthma control than those patients randomized to SINGULAIR alone or placebo alone as indicated by FEV_1, daytime asthma symptoms, PEFR, nocturnal awakenings due to asthma, and "as-needed" β-agonist requirements.

In adult patients with asthma with documented aspirin sensitivity, nearly all of whom were receiving concomitant inhaled and/or oral corticosteroids, a 4-week, randomized, parallel-group trial (n=80)

demonstrated that SINGULAIR, compared with placebo, resulted in significant improvement in parameters of asthma control. The magnitude of effect of SINGULAIR in aspirin-sensitive patients was similar to the effect observed in the general population of asthma patients studied. The effect of SINGULAIR on the bronchoconstrictor response to aspirin or other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients has not been evaluated *[see Warnings and Precautions (5.3)]*.

14.2 Exercise-Induced Bronchoconstriction (EIB)

Exercise-Induced Bronchoconstriction (Adults, Adolescents, and Pediatric Patients 6 years of age and older)

The efficacy of SINGULAIR, 10 mg, when given as a single dose 2 hours before exercise for the prevention of EIB was investigated in three (U.S. and Multinational), randomized, double-blind, placebo-controlled crossover studies that included a total of 160 adult and adolescent patients 15 years of age and older with EIB. Exercise challenge testing was conducted at 2 hours, 8.5 or 12 hours, and 24 hours following administration of a single dose of study drug (SINGULAIR 10 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV_1 following the 2 hours post-dose exercise challenge in all three studies (Study A, Study B, and Study C). In Study A, a single dose of SINGULAIR 10 mg demonstrated a statistically significant protective benefit against EIB when taken 2 hours prior to exercise. Some patients were protected from EIB at 8.5 and 24 hours after administration; however, some patients were not. The results for the mean maximum percent fall at each timepoint in Study A are shown in TABLE 3 and are representative of the results from the other two studies.

Table 3: Mean Maximum Percent Fall in FEV_1 Following Exercise Challenge in Study A (N=47) ANOVA Model

Time of exercise challenge following medication administration	Mean Maximum percent fall in FEV_1*		Treatment difference % for SINGULAIR versus Placebo (95% CI)*
	SINGULAIR	Placebo	
2 hours	13	22	-9 (-12, -5)
8.5 hours	12	17	-5 (-9, -2)
24 hours	10	14	-4 (-7, -1)

*Least squares-mean

The efficacy of SINGULAIR 5-mg chewable tablets, when given as a single dose 2 hours before exercise for the prevention of EIB, was investigated in one multinational, randomized, double-blind, placebo-controlled crossover study that included a total of 64 pediatric patients 6 to 14 years of age with EIB. Exercise challenge testing was conducted at 2 hours and 24 hours following administration of a single dose of study drug (SINGULAIR 5 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV_1 following the 2 hours post-dose exercise challenge. A single dose of SINGULAIR 5 mg demonstrated a statistically significant protective benefit against EIB when taken 2 hours prior to exercise (TABLE 4). Similar results were shown at 24 hours post-dose (a secondary endpoint). Some patients were protected from EIB at 24 hours after administration; however, some patients were not. No timepoints were assessed between 2 and 24 hours post-dose.

Table 4: Mean Maximum Percent Fall in FEV_1 Following Exercise Challenge in Pediatric Patients (N=64) ANOVA Model

Time of exercise challenge following medication administration	Mean Maximum percent fall in FEV_1*		Treatment difference % for SINGULAIR versus Placebo (95% CI)*
	SINGULAIR	Placebo	
2 hours	15	20	-5 (-9, -1)
24 hours	13	17	-4 (-7, -1)

*Least squares-mean

The efficacy of SINGULAIR for prevention of EIB in patients below 6 years of age has not been established.

Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.

In a 12-week, randomized, double-blind, parallel group study of 110 adult and adolescent asthmatics 15 years of age and older, with a mean baseline FEV_1 percent of predicted of 83% and with documented exercise-induced exacerbation of asthma, treatment with SINGULAIR, 10 mg, once daily in the evening, resulted in a statistically significant reduction in mean maximal percent fall in FEV_1 and mean time to recovery to within 5% of the pre-exercise FEV_1. Exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose). This effect was maintained throughout the 12-week treatment period indicating that tolerance did not occur. SINGULAIR did not, however, prevent clinically significant deterioration in maximal percent fall in FEV_1 after exercise (i.e., ≥20% decrease from pre-exercise baseline) in 52% of patients studied. In a separate crossover study in adults, a similar effect was observed after two once-daily 10-mg doses of SINGULAIR.

In pediatric patients 6 to 14 years of age, using the 5-mg chewable tablet, a 2-day crossover study demonstrated effects similar to those observed in adults when exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose).

14.3 Allergic Rhinitis (Seasonal and Perennial)

Seasonal Allergic Rhinitis

The efficacy of SINGULAIR tablets for the treatment of seasonal allergic rhinitis was investigated in 5 similarly designed, randomized, double-blind, parallel-group, placebo- and active-controlled (loratadine) trials conducted in North America. The 5 trials enrolled a total of 5029 patients, of whom 1799 were treated with SINGULAIR tablets. Patients were 15 to 82 years of age with a history of seasonal allergic rhinitis, a positive skin test to at least one relevant seasonal allergen, and active symptoms of seasonal allergic rhinitis at study entry.

The period of randomized treatment was 2 weeks in 4 trials and 4 weeks in one trial. The primary outcome variable was mean change from baseline in daytime nasal symptoms score (the average of individual scores of nasal congestion, rhinorrhea, nasal itching, sneezing) as assessed by patients on a 0-3 categorical scale.

Four of the five trials showed a significant reduction in daytime nasal symptoms scores with SINGULAIR 10-mg tablets compared with placebo. The results of one trial are shown below. The median age in this trial was 35.0 years (range 15 to 81); 65.4% were females and 34.6% were males. The ethnic/racial distribution in this study was 83.1% Caucasian, 6.4% other origins, 5.8% Black, and 4.8% Hispanic. The mean changes from baseline in daytime nasal symptoms score in the treatment groups that received SINGULAIR tablets, loratadine, and placebo are shown in TABLE 5. The remaining three trials that demonstrated efficacy showed similar results.

Table 5: Effects of SINGULAIR on Daytime Nasal Symptoms Score* in a Placebo- and Active-controlled Trial in Patients with Seasonal Allergic Rhinitis (ANCOVA Model)

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (344)	2.09	-0.39	-0.13† (-0.21, -0.06)
Placebo (351)	2.10	-0.26	N.A.
Active Control‡ (Loratadine 10 mg) (599)	2.06	-0.46	-0.24† (-0.31, -0.17)

* Average of individual scores of nasal congestion, rhinorrhea, nasal itching, sneezing as assessed by patients on a 0-3 categorical scale.

† Statistically different from placebo ($p \leq 0.001$).

‡ The study was not designed for statistical comparison between SINGULAIR and the active control (loratadine).

Perennial Allergic Rhinitis

The efficacy of SINGULAIR tablets for the treatment of perennial allergic rhinitis was investigated in 2 randomized, double-blind, placebo-controlled studies conducted in North America and Europe. The two studies enrolled a total of 3357 patients, of whom 1632 received SINGULAIR 10-mg tablets. Patients 15 to 82 years of age with perennial allergic rhinitis as confirmed by history and a positive skin test to at least one relevant perennial allergen (dust mites, animal dander, and/or mold spores), who had active symptoms at the time of study entry, were enrolled.

In the study in which efficacy was demonstrated, the median age was 35 years (range 15 to 81); 64.1% were females and 35.9% were males. The ethnic/racial distribution in this study was 83.2% Caucasian, 8.1% Black, 5.4% Hispanic, 2.3% Asian, and 1.0% other origins. SINGULAIR 10-mg tablets once daily was shown to significantly reduce symptoms of perennial allergic rhinitis over a 6-week treatment period (TABLE 6); in this study the primary outcome variable was mean change from baseline in daytime nasal symptoms score (the average of individual scores of nasal congestion, rhinorrhea, and sneezing).

Table 6: Effects of SINGULAIR on Daytime Nasal Symptoms Score* in a Placebo-controlled Trial in Patients with Perennial Allergic Rhinitis (ANCOVA Model)

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (1000)	2.09	-0.42	-0.08† (-0.12, -0.04)
Placebo (980)	2.10	-0.35	N.A.

* Average of individual scores of nasal congestion, rhinorrhea, sneezing as assessed by patients on a 0-3 categorical scale.
† Statistically different from placebo ($p \leq 0.001$).

The other 6-week study evaluated SINGULAIR 10 mg (n=626), placebo (n=609), and an active-control (cetirizine 10 mg; n=120). The primary analysis compared the mean change from baseline in daytime nasal symptoms score for SINGULAIR vs. placebo over the first 4 weeks of treatment; the study was not designed for statistical comparison between SINGULAIR and the active-control. The primary outcome variable included nasal itching in addition to nasal congestion, rhinorrhea, and sneezing. The estimated difference between SINGULAIR and placebo was -0.04 with a 95% CI of (-0.09, 0.01). The estimated difference between the active-control and placebo was -0.10 with a 95% CI of (-0.19, -0.01).

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3841 — SINGULAIR Oral Granules, 4 mg, are white granules with 500 mg net weight, packed in a child-resistant foil packet. They are supplied as follows:

NDC 0006-3841-30 unit of use carton with 30 packets.

SINGULAIR Tablets, 4 mg, are pink, oval, bi-convex-shaped chewable tablets. They are supplied as either No. 3796 or No. 6628:

No. 3796 — with code MRK 711 on one side and SINGULAIR on the other:

NDC 0006-0711-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0711-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant.

No. 6628 — with code MSD 711 on one side and SINGULAIR on the other:

NDC 0006-1711-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-1711-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant.

SINGULAIR Tablets, 5 mg, are pink, round, bi-convex-shaped chewable tablets. They are supplied as either No. 3760 or No. 6543:

No. 3760 — with code MRK 275 on one side and SINGULAIR on the other:

NDC 0006-0275-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0275-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant.

No. 6543 — with code MSD 275 on one side and SINGULAIR on the other:

NDC 0006-9275-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-9275-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-9275-82 bulk packaging high-density polyethylene (HDPE) bottles of 1000 with a non-child-resistant white plastic closure with a wax paper/pulp liner, an aluminum foil induction seal, and silica gel desiccant.

SINGULAIR Tablets, 10 mg, are beige, rounded square-shaped, film-coated tablets. They are supplied as either No. 3761 or No. 6558:

No. 3761 — with code MRK 117 on one side and SINGULAIR on the other:

NDC 0006-0117-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0117-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-0117-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister pack of 100.

No. 6558 — with code MSD 117 on one side and SINGULAIR on the other:

NDC 0006-9117-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-9117-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and silica gel desiccant

NDC 0006-9117-80 bulk packaging high-density polyethylene (HDPE) bottles of 8000 with a non-child-resistant white plastic closure with a wax paper/pulp liner, an aluminum foil induction seal, and silica gel desiccant.

Storage

Store SINGULAIR 4-mg oral granules, 4-mg chewable tablets, 5-mg chewable tablets and 10-mg film-coated tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in original package.

Storage for Bulk Bottles

Store bottles of 1000 SINGULAIR 5-mg chewable tablets and 8000 SINGULAIR 10-mg film-coated tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in original container. When product container is subdivided, repackage into a well-closed, light-resistant container.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Information for Patients

- Patients should be advised to take SINGULAIR daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.
- Patients should be advised that oral SINGULAIR is not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β-agonist medication available to treat asthma exacerbations. Patients who have exacerbations of asthma after exercise should be instructed to have available for rescue a short-acting inhaled β-agonist. Daily administration of SINGULAIR for the chronic treatment of asthma has not been established to prevent acute episodes of EIB.
- Patients should be advised that, while using SINGULAIR, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed.

- Patients receiving SINGULAIR should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients should be instructed to notify their physician if neuropsychiatric events occur while using SINGULAIR.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR.
- Phenylketonuric patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame).

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For patent information: www.merck.com/product/patent/home.html

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Current Rx Singulair Patient Package Insert

Patient Information
SINGULAIR® (SING-u-lair)
(montelukast sodium)
Tablets

SINGULAIR®
(montelukast sodium)
Chewable Tablets

SINGULAIR®
(montelukast sodium)
Oral Granules

Read the Patient Information Leaflet that comes with SINGULAIR® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is SINGULAIR?

- SINGULAIR is a prescription medicine that blocks substances in the body called leukotrienes. This may help to improve symptoms of asthma and allergic rhinitis. SINGULAIR does not contain a steroid.

SINGULAIR is used to:

1. Prevent asthma attacks and for the long-term treatment of asthma in adults and children ages 12 months and older.

   Do not take SINGULAIR if you need relief right away for a sudden asthma attack. If you get an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.

2. Prevent exercise-induced asthma in people 6 years of age and older.

3. Help control the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose). SINGULAIR is used to treat:
   - outdoor allergies that happen part of the year (seasonal allergic rhinitis) in adults and children ages 2 years and older, **and**
   - indoor allergies that happen all year (perennial allergic rhinitis) in adults and children ages 6 months and older.

Who should not take SINGULAIR?

Do not take SINGULAIR if you are allergic to any of its ingredients.

See the end of this leaflet for a complete list of the ingredients in SINGULAIR.

What should I tell my healthcare provider before taking SINGULAIR?

Before taking SINGULAIR, tell your healthcare provider if you:
- are allergic to aspirin
- have phenylketonuria. SINGULAIR chewable tablets contain aspartame, a source of phenylalanine

- have any other medical conditions
- are pregnant or plan to become pregnant. Talk to your doctor if you are pregnant or plan to become pregnant, as SINGULAIR may not be right for you.
- are breast-feeding or plan to breast-feed. It is not known if SINGULAIR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking SINGULAIR.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how SINGULAIR works, or SINGULAIR may affect how your other medicines work.

How should I take SINGULAIR?

For anyone who takes SINGULAIR:

- Take SINGULAIR exactly as prescribed by your healthcare provider. Your healthcare provider will tell you how much SINGULAIR to take, and **when to take it.**
- Do not stop taking SINGULAIR or change when you take it without talking with your healthcare provider.
- You can take SINGULAIR with food or without food. See the information below in the section "How should I give SINGULAIR oral granules to my child?" for information about what foods and liquids can be taken with SINGULAIR oral granules.
- **If you or your child misses a dose of SINGULAIR, just take the next dose at your regular time.** Do not take 2 doses at the same time.
- If you take too much SINGULAIR, call your healthcare provider or a Poison Control Center right away.

For adults and children 12 months of age and older with asthma:

- Take SINGULAIR 1 time each day, in the evening. Continue to take SINGULAIR every day for as long as your healthcare provider prescribes it, even if you have no asthma symptoms.
- Tell your healthcare provider right away if your asthma symptoms get worse, or if you need to use your rescue inhaler medicine more often for asthma attacks.
- **Do not take SINGULAIR if you need relief right away from a sudden asthma attack.** If you get an asthma attack, you should follow the instructions your healthcare provider gave you for treating asthma attacks.
- Always have your rescue inhaler medicine with you for asthma attacks.
- Do not stop taking or lower the dose of your other asthma medicines unless your healthcare provider tells you to.

For patients 6 years of age and older for the prevention of exercise-induced asthma:

- Take SINGULAIR at least 2 hours before exercise.
- Always have your rescue inhaler medicine with you for asthma attacks.
- If you take SINGULAIR every day for chronic asthma or allergic rhinitis, **do not** take another dose to prevent exercise-induced asthma. Talk to your healthcare provider about your treatment for exercise-induced asthma.
- **Do not take 2 doses of SINGULAIR within 24 hours (1 day).**

For adults and children 2 years of age and older with seasonal allergic rhinitis, or for adults and children 6 months of age and older with perennial allergic rhinitis:

- Take SINGULAIR 1 time each day, at about the same time each day.

How should I give SINGULAIR oral granules to my child?

Give SINGULAIR oral granules to your child exactly as instructed by your healthcare provider.

Do not open the packet until ready to use.

SINGULAIR 4-mg oral granules can be given:

- right in the mouth; or
- dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk; or
- mixed with 1 spoonful of one of the following soft foods at cold or room temperature: applesauce, mashed carrots, rice, or ice cream.

Give the child all of the mixture right away, within 15 minutes.

Do not store any leftover SINGULAIR mixture (oral granules mixed with food, baby formula, or breast milk) for use at a later time. Throw away any unused portion.

Do not mix SINGULAIR oral granules with any liquid drink other than baby formula or breast milk. Your child may drink other liquids after swallowing the mixture.

What is the dose of SINGULAIR?

The dose of SINGULAIR prescribed for your or your child's condition is based on age:

- 6 to 23 months: one packet of 4-mg oral granules.
- 2 to 5 years: one 4-mg chewable tablet or one packet of 4-mg oral granules.
- 6 to 14 years: one 5-mg chewable tablet.
- 15 years and older: one 10-mg tablet.

What should I avoid while taking SINGULAIR?

If you have asthma and aspirin makes your asthma symptoms worse, continue to avoid taking aspirin or other medicines called non-steroidal anti-inflammatory drugs (NSAIDs) while taking SINGULAIR.

What are the possible side effects of SINGULAIR?

SINGULAIR may cause serious side effects.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - attention problems
  - bad or vivid dreams
  - depression
  - disorientation (confusion)
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - irritability
  - memory problems
  - restlessness
  - sleep walking
  - suicidal thoughts and actions (including suicide)
  - tremor
  - trouble sleeping

- **Increase in certain white blood cells (eosinophils) and possible inflamed blood vessels throughout the body (systemic vasculitis).** Rarely, this can happen in people with asthma who take SINGULAIR. This sometimes happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered.
  Tell your healthcare provider right away if you get one or more of these symptoms:
  - a feeling of pins and needles or numbness of arms or legs
  - a flu-like illness
  - rash

- severe inflammation (pain and swelling) of the sinuses (sinusitis)

The most common side effects with SINGULAIR include:

- upper respiratory infection
- fever
- headache
- sore throat
- cough
- stomach pain
- diarrhea
- earache or ear infection
- flu
- runny nose
- sinus infection

Other side effects with SINGULAIR include:

- increased bleeding tendency, low blood platelet count
- allergic reactions [including swelling of the face, lips, tongue, and/or throat (which may cause trouble breathing or swallowing), hives and itching]
- dizziness, drowsiness, pins and needles/numbness, seizures (convulsions or fits)
- palpitations
- nose bleed, stuffy nose, swelling (inflammation) of the lungs
- heartburn, indigestion, inflammation of the pancreas, nausea, stomach or intestinal upset, vomiting
- hepatitis
- bruising, rash, severe skin reactions (erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis) that may occur without warning
- joint pain, muscle aches and muscle cramps
- tiredness, swelling

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of SINGULAIR. For more information ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SINGULAIR?

- Store SINGULAIR at 59°F to 86°F (15°C to 30°C).
- Keep SINGULAIR in the container it comes in.
- Keep SINGULAIR in a dry place and away from light.

General Information about the safe and effective use of SINGULAIR

Medicines are sometimes prescribed for purposes other than those mentioned in Patient Information Leaflets. Do not use SINGULAIR for a condition for which it was not prescribed. Do not give SINGULAIR to other people even if they have the same symptoms you have. It may harm them. **Keep SINGULAIR and all medicines out of the reach of children.**

This leaflet summarizes information about SINGULAIR. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about SINGULAIR that is written for health professionals. For more information, call the Merck National Service Center at 1-800-NSC-Merck (1-800-672-6372).

What are the ingredients in SINGULAIR?

Active ingredient: montelukast sodium

Inactive ingredients:

- 4-mg oral granules: mannitol, hydroxypropyl cellulose, and magnesium stearate.
- 4-mg and 5-mg chewable tablets: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

  People with Phenylketonuria: SINGULAIR 4-mg chewable tablets contain 0.674 mg of phenylalanine, and SINGULAIR 5-mg chewable tablets contain 0.842 mg of phenylalanine.
- 10-mg tablet: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating contains: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

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Appendix 2 Individual Pivotal Study Data: Nasal and Eye Symptoms Scores and RQoL Questionnaire Data

Rx Singulair has been approved for SAR in 2002 and PAR in 2005. The efficacy of montelukast for AR has been established based on the primary endpoints of nasal symptoms (rhinorrhea, pruritus, sneezing, and nasal congestion) and supported by several secondary endpoints.

Typically FDA approves Rx indications based on primary endpoints, which are routinely listed in the prescription label. All other endpoints that comprise a development program are usually not listed in the Rx label, unless an explicit plan (and/or analytic approach) has been pre-specified. In recent years, more sophisticated statistical methodology has been leveraged to support the addition of secondary endpoints to product labeling (i.e., pre-specified statistical approaches to support making multiple comparisons, sometimes called "multiplicity adjustments"). However, in the late 1990s and early 2000s (i.e., the time of the Rx Singulair clinical development program), these approaches were less commonly used to support product labeling claims. Thus, since the development program did not pre-specify an approach for secondary endpoints to be added to the labeling, the label for Rx Singulair does not include claims for eye symptoms relief.

The requested inclusion of "itchy/watery eyes" to the OTC Drug Facts label is supported by the efficacy demonstrated via the overall Daytime Eye Symptoms score and the individual eye symptom scores of "tearing eyes" and "itchy eyes," assessed in the 3 pivotal SAR studies**.** Similar to what was previously described in **Section 4.0** for the primary endpoint Daytime Nasal Symptoms score, variability in the efficacy of Rx Singulair on the overall Daytime Eye Symptoms score as well as the individual symptoms scores was observed in the pivotal SAR studies. Significant efficacy was demonstrated for the overall Daytime Eye Symptoms score as well as the individual eye symptoms scores in 2 of the 3 pivotal studies (**Tables 27** and **29**)**.**

Patients were asked to rate their individual eye symptoms using the scale below, which is a common AR rating system that has been utilized in clinical trials and is adapted from the FDA Draft Guidance.[2]

- 0 = none (not noticeable)
- 1 = mild (symptom noticeable but not bothersome)
- 2 = moderate (symptom noticeable and bothersome some of the time)
- 3 = severe (symptom bothersome most of the time and/or very bothersome some of the time)

To support the clinical relevancy of these efficacy measures, the improvement in the burden of these symptoms was assessed. Patients in each of the 4 pivotal AR studies were asked to self-assess their quality of life using a validated questionnaire[28] by Juniper et al. at baseline and end of treatment. The

Rhinoconjunctivitis Quality of Life (RQoL) questionnaire asks patients to use a 7-point scale (0 [very much better] to 6 [very much worse]) to assess the burden of their symptoms as it relates to 28 items within 7 separate domains, or categories. These domains have been validated to be important to patients with AR and measure the impact of AR on activities, sleep, non-nose/non-eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotions.

Montelukast demonstrated significantly greater treatment benefit over placebo in overall RQoL score (mean of all 7 domains) in 3 of the 4 pivotal studies (**Table 30**). The request to include “itchy/watery eyes” on the OTC label is further supported by the significantly greater treatment benefit over placebo in the specific Eye Symptoms domain of the RQoL assessed in the 4 pivotal studies, as mentioned previously in **Section 4.2** (**Table 8**).

Table 26 Individual Pivotal SAR Studies: Overall Daytime Nasal Symptoms Scores‡

	N†		Mean Baseline (Score)		Change From Baseline (Score) (Mean ± SE)		Difference in LS Means (95% CI)
	Monte-lukast	Placebo	Monte-lukast	Placebo	Montelukast	Placebo	Montelukast Minus Placebo
Phase III Studies							
Pivotal							
Protocol 162	344	351	2.09	2.10	-0.39±0.03	-0.26±0.03	-0.13*** (-0.21, -0.06)
Protocol 192	326	331	2.14	2.09	-0.38±0.03	-0.30±0.03	-0.06 (-0.14, 0.01)
Protocol 235	519	521	2.10	2.14	-0.39±0.02	-0.31±0.02	-0.09** (-0.16, -0.03)
Pooled Studies							
Pivotal Phase III	1189	1203	2.11	2.12	-0.38±0.02	-0.29±0.02	-0.10*** (-0.14, -0.05)

‡Daytime Nasal Symptoms Score = average of the following 4 symptoms (congestion, rhinorrhea, itching, sneezing)
*p≤0.05, *** p≤0.001 compared with placebo.
† N = Number of patients included in the modified intention-to-treat (mITT) analysis.
LS Means = Least-Squares Means; SE = Standard Error; CI = Confidence Interval.
Source: NDA 20-829/S-017 (Merck: Montelukast Sodium – Seasonal AR); Clinical and Statistical Documentation; Section D, Table D-4, Table D-11.

Table 27 Individual Pivotal SAR Studies: Overall Daytime Eye Symptoms Scores‡

	N†		Mean Baseline (Score)		Change From Baseline (Score) (Mean ± SE)		Difference in LS Means (95% CI)
Study	Monte-lukast	Placebo	Monte-lukast	Placebo	Montelukast	Placebo	Montelukast Minus Placebo
Phase III Studies							
Pivotal							
Protocol 162	344	351	1.39	1.44	-0.28±0.03	-0.15±0.03	-0.14*** (-0.22,-0.06)
Protocol 192	326	331	1.46	1.47	-0.29±0.03	-0.22±0.03	-0.07 (-0.14, 0.01)
Protocol 235	519	521	1.49	1.53	-0.30±0.02	-0.24±0.02	-0.07* (-0.13,-0.01)
Pooled Studies							
Pivotal Phase III	1189	1203	1.45	1.48	-0.29±0.02	-0.21±0.02	-0.09*** (-0.13,-0.05)

‡Daytime Eye Symptoms Score = average of the following 4 symptoms (itchy eyes, tearing eyes, red eyes, puffy eyes)
*p≤0.05, *** p≤0.001 compared with placebo.
† N = Number of patients included in the modified intention-to-treat (mITT) analysis.
LS Means = Least-Squares Means; SE = Standard Error; CI = Confidence Interval.
Source: NDA 20-829/S-017 (Merck: Montelukast Sodium – Seasonal AR); Clinical and Statistical Documentation; Section D, Table D-4, Table D-11.

Table 28 Individual Pivotal SAR Studies: Individual Daytime Nasal Symptoms Scores

Study	N†		Mean Baseline (Score)		Change From Baseline (Score) (Mean ± SE)		Difference in LS Means (95% CI) Montelukast Minus Placebo	
	Monte-lukast	Placebo	Monte-lukast	Placebo	Montelukast	Placebo		
Congestion								
Protocol 162	344	351	2.35	2.34	-0.38±0.03	-0.28±0.03	-0.10*	(-0.18,-0.01)
Protocol 192	326	331	2.38	2.40	-0.39±0.03	-0.28±0.03	-0.11*	(-0.20,-0.03)
Protocol 235	519	521	2.33	2.38	-0.37±0.03	-0.30±0.03	-0.09**	(-0.16,-0.02)
Pooled Pivotal‡	1189	1203	2.35	2.37	-0.38±0.02	-0.29±0.02	-0.10***	(-0.14,-0.05)
Rhinorrhea								
Protocol 162	344	351	2.10	2.16	-0.41±0.04	-0.30±0.03	-0.14**	(-0.24,-0.05)
Protocol 192	326	331	2.18	2.12	-0.39±0.04	-0.34±0.04	-0.02	(-0.11, 0.07)
Protocol 235	519	521	2.11	2.12	-0.42±0.03	-0.31±0.03	-0.11**	(-0.19,-0.04)
Pooled Pivotal‡	1189	1203	2.12	2.13	-0.41±0.02	-0.32±0.02	-0.10***	(-0.15,-0.05)
Itching								
Protocol 162	344	351	1.97	1.98	-0.37±0.04	-0.26±0.03	-0.12*	(-0.21,-0.02)
Protocol 192	326	331	2.05	1.99	-0.38±0.03	-0.33±0.03	-0.03	(-0.13, 0.06)
Protocol 235	519	521	2.03	2.10	-0.39±0.03	-0.35±0.03	-0.06	(-0.14, 0.01)
Pooled Pivotal‡	1189	1203	2.02	2.04	-0.38±0.02	-0.32±0.02	-0.07**	(-0.12,-0.02)
Sneezing								
Protocol 162	344	351	1.95	1.93	-0.37±0.04	-0.19±0.03	-0.18**	(-0.27,-0.08)
Protocol 192	326	331	1.94	1.86	-0.37±0.04	-0.26±0.04	-0.07	(-0.17, 0.02)
Protocol 235	519	521	1.94	1.96	-0.37±0.03	-0.26±0.03	-0.11**	(-0.19,-0.03)
Pooled Pivotal‡	1189	1203	1.94	1.92	-0.37±0.02	-0.24±0.02	-0.12**	(-0.17,-0.07)

* p≤0.05, ** p≤0.01, *** p≤0.001 compared with placebo.
† Number of patients included in the modified intention-to-treat analysis.
‡ Protocols 162, 192, and 235 combined.
LS Means = Least-Squares Means; SE = Standard Error; CI = Confidence Interval.

Source: NDA 20-829/S-017 (Merck Montelukast Sodium – Seasonal AR); Clinical and Statistical Documentation; Section D, Table D-17.

Table 29 Individual Pivotal SAR Studies: Individual Daytime Eye Symptoms Scores

Study	N†		Mean Baseline (Score)		Change From Baseline (Score) (Mean ± SE)		Difference in LS Means (95% CI)
	Monte-lukast	Placebo	Monte-lukast	Placebo	Montelukast	Placebo	Montelukast Minus Placebo
Tearing Eyes							
Protocol 162	344	351	1.36	1.39	-0.29±0.03	-0.11±0.03	-0.19*** (-0.28,-0.09)
Protocol 192	326	331	1.46	1.45	-0.29±0.03	-0.22±0.03	-0.06 (-0.15, 0.03)
Protocol 235	519	521	1.51	1.47	-0.32±0.03	-0.21±0.03	-0.10* (-0.17,-0.02)
Pooled Pivotal‡	1189	1203	1.46	1.44	-0.30±0.02	-0.18±0.02	-0.11*** (-0.16,-0.06)
Itchy Eyes							
Protocol 162	344	351	1.83	1.85	-0.34±0.04	-0.20±0.04	-0.15** (-0.24,-0.05)
Protocol 192	326	331	1.84	1.84	-0.35±0.04	-0.25±0.04	-0.10* (-0.20,-0.01)
Protocol 235	519	521	1.92	1.99	-0.36±0.03	-0.34±0.03	-0.04 (-0.12, 0.03)
Pooled Pivotal‡	1189	1203	1.87	1.91	-0.35±0.02	-0.28±0.02	-0.09*** (-0.14,-0.04)
Red Eyes							
Protocol 162	344	351	1.27	1.36	-0.26±0.03	-0.17±0.03	-0.12** (-0.21,-0.03)
Protocol 192	326	331	1.38	1.37	-0.29±0.03	-0.25±0.03	-0.05 (-0.13, 0.04)
Protocol 235	518	521	1.32	1.40	-0.25±0.03	-0.22±0.03	-0.05 (-0.12, 0.02)
Pooled Pivotal‡	1188	1203	1.32	1.38	-0.26±0.02	-0.21±0.02	-0.07** (-0.11,-0.02)
Puffy Eyes							
Protocol 162	344	351	1.10	1.15	-0.21±0.03	-0.10±0.03	-0.13** (-0.22,-0.04)
Protocol 192	326	331	1.16	1.21	-0.23±0.03	-0.18±0.03	-0.06 (-0.15, 0.02)
Protocol 235	518	521	1.21	1.25	-0.25±0.03	-0.18±0.03	-0.09* (-0.16,-0.02)
Pooled Pivotal‡	1188	1203	1.16	1.21	-0.23±0.02	-0.16±0.02	-0.09*** (-0.14,-0.05)

* p≤0.05, ** p≤0.01, *** p≤0.001 compared with placebo.
† Number of patients included in the modified intention-to-treat analysis.
‡ Protocols 162, 192, and 235 combined.
LS Means = Least-Squares Means; SE = Standard Error; CI = Confidence Interval.

Source: NDA 20-829/S-017 (Merck Montelukast Sodium – Seasonal AR); Clinical and Statistical Documentation; Section D, Table D-12.

Table 30 Overall RQoL in AR Pivotal Studies (Average of the 7 Domains)

A. Overall RQoL, Seasonal AR

Study	N†		Mean Baseline (Score)		Change From Baseline (Score) (Mean ± SE)		Difference in LS Means (95% CI)
	Monte-lukast	Placebo	Monte-lukast	Placebo	Montelukast	Placebo	Montelukast Minus Placebo
Phase III Studies							
Pivotal							
Protocol 162	344	348	3.19	3.29	-0.90±0.06	-0.70±0.06	-0.24** (-0.40,-0.08)
Protocol 192	324	330	3.19	3.18	-0.87±0.06	-0.77±0.06	-0.10 (-0.26, 0.06)
Protocol 235	518	516	3.22	3.29	-0.93±0.05	-0.71±0.05	-0.24*** (-0.38,-0.11)
Pooled Studies							
Pivotal Phase III	1186	1194	3.21	3.26	-0.91±0.03	-0.72±0.03	-0.20*** (-0.29,-0.12)

** p≤0.01, *** p≤0.001 compared with placebo.
N = Number of patients included in the modified intention-to-treat (mITT) analysis.
LS Means = Least-Squares Means; SE = Standard Error; CI = Confidence Interval.
Reference: NDA 20-829/S-017 (Merck: Montelukast Sodium – Seasonal Allergic Rhinitis); Clinical and Statistical Documentation; Section D, Table D-13.

B. Overall RQoL, Perennial AR

Treatment Group	N	Mean (Score)		Change from Baseline			
		Baseline	Treatment Period	Mean	SD	LS Mean	95% CI for LS Mean
Montelukast 10 mg	977	2.94	2.13	-0.81	1.14	-0.84	(-0.91,-0.77)
Placebo	969	2.97	2.29	-0.68	1.14	-0.69	(-0.76,-0.62)

Comparison Between Treatment Groups	p-Value	LS Mean	95% CI for Difference
Montelukast 10 mg versus Placebo	≤0.001	-0.15	(-0.24,-0.06)

p-Value for Effect: Study Center: ≤0.001 Baseline Value: ≤0.001
Root Mean-Square Error: 1.024
CI: Confidence Interval; LS Mean: Least-Squares Mean; SD: Standard Deviation.

Source: CSR P265

Appendix 3 Patient Self-Rated Global Evaluation of AR (GEoAR)

The overall clinical relevance of montelukast for the treatment of AR has been measured by the patient self-rated global evaluation of AR (GEoAR), in which patients were asked to answer one question, “Compared to when I entered the study, my allergic symptoms are …,” using a 7-point scale ranging from 0 (very much better) to 6 (very much worse). The GEoAR provides a simple overall measurement of the patient-perceived benefit of the therapy. Results are consistent with and provide additional validation of the patient’s self-rated nasal and the ocular symptom scores, as well as the RQoL data. This global measure does not differentiate which symptoms are considered more important than others when patients are determining their overall GEoAR score.

Significantly better GEoAR score was observed for montelukast versus placebo in Study 162 (SAR; $p<0.001$), Study 235 (SAR; $p<0.001$), and Study 265 (PAR; $p=0.010$); but not in Study 192 (SAR; $p\leq0.099$) (**Table 31**).

Table 31 Global Evaluations of AR (GEoAR): Patient Assessment

A. Patient GEoAR, Seasonal AR

	N†		Mean Treatment Score ± SE		Difference in LS Means (95% CI)
	Montelukast	Placebo	Montelukast	Placebo	Montelukast Minus Placebo
Phase III Studies					
Pivotal					
Protocol 162	343	347	2.13±0.08	2.56±0.08	-0.42*** (-0.64,-0.20)
Protocol 192	324	333	2.38±0.08	2.57±0.08	-0.19 (-0.42, 0.04)
Protocol 235	519	517	2.13±0.07	2.45±0.07	-0.31*** (-0.50,-0.13)
Pooled Studies					
Pivotal Phase III	1186	1197	2.20±0.04	2.52±0.04	-0.31*** (-0.43,-0.19)

*** p≤0.001 compared with placebo.
† N = Number of patients included in the modified intention-to-treat (mITT) analysis.
LS Means = Least-Squares Means; SE = Standard Error; CI = Confidence Interval.
Reference: NDA 20-829/S-017 (Merck: Montelukast Sodium – Seasonal Allergic Rhinitis); Clinical and Statistical Documentation; Section D, Table D-14.

B. Patient GEoAR, Perennial AR

Treatment Group	N	Global Evaluation Score			
		Mean	SD	LS Mean	95% CI for LS Mean
Montelukast 10 mg	977	2.28	1.29	2.27	(2.18, 2.35)
Placebo	969	2.44	1.29	2.42	(2.33, 2.51)

Comparison Between Treatment Groups	p-Value	LS Mean	95% CI for Difference
Montelukast 10 mg versus Placebo	0.007	-0.15	(-0.27,-0.04)

p-Value for Effect: Study Center: ≤0.001
Root Mean-Square Error: 1.248
CI: Confidence Interval; LS Mean: Least-Squares Mean; SD: Standard Deviation.

Source: CSR P265

Appendix 4 Summary of Analyses in Response to FDA Investigation of Behavior/Mood Changes Possibly Related to Leukotriene-Modifying Agents

In 2008, FDA posted an "Early Communication About an Ongoing Safety Review of Montelukast (Singulair)"[37] and requested all 3 manufacturers (Merck, AstraZeneca, and Cornerstone Therapeutics) of leukotriene-modifying agents to conduct analyses of their controlled clinical trial data with regard to behavior and mood-related adverse events (BRAEs). In response to the request, Merck reviewed its clinical trial databases for specific AEs related to neuropsychiatric events, as described in **Section 5.3.2.1**, and conducted 2 analyses (**Table 32**). Subsequently in 2009, Merck chose to publish the results of these analyses (**Tables 33** and **34**) that were shared previously with the FDA in two publications.[43,44]

Table 32 Analyses in Response to FDA Investigation of Behavior/Mood Changes Possibly Related to Leukotriene-Modifying Agents

	Methods
First Publication[43] (J Allergy Clin Immunol 2009;124:691-6)	1. Retrospective descriptive review of investigator-reported AEs related to suicidality from 116 Merck-sponsored clinical trials (double-blind and open-label, adult and pediatric, and single- and multiple-dose studies) completed as of March 2008.
	2. Focused, adjudicated analysis (using the Columbia Classification Algorithm of Suicide Assessment, or C-CASA[40]) of possibly suicidality related adverse events (PSRAEs) from a pre-specified set of data from 41 Merck-sponsored placebo-controlled clinical trials completed as of April 2008.
Second Publication[44] (J Allergy Clin Immunol 2009;124:699-706)	1. Retrospective review of behavior related adverse events (BRAEs) in 46 placebo-controlled clinical trials.

First Publication

Results detailed in the first publication of Merck-sponsored clinical trial data, using the retrospective descriptive review method (Method 1), indicated two reports of suicidality (one suicide attempt and one suicidal ideation), both deemed not-drug related by the investigators, in montelukast-treated patients (n=20,131). One report of suicidality existed in the placebo arm (n=9,287) and three reports of suicide attempt in the active-control groups (n=8,346). No completed suicides were reported in any study (**Table 33**).

Table 33 Results, Retrospective Descriptive Review of AEs Possibly-Related to Suicidality in 116 Merck-Sponsored Trials

Study Arms	116 Placebo-Control, Active-Control, or Open-Label Studies
Montelukast arm	1 subject: 18 yo female, 2 reports (self-harm behavior and suicide attempt)
Placebo-Control arm	1 subject: intentional self-injury (bite in mouth) in a 4 yo patient
Active-Control arm	3 subjects: 20 yo female (suicide attempt); 30 yo female (suicide attempt); 16 yo female (suicide attempt)

The C-CASA analysis of adjudicated PSRAEs (Method 2) was also discussed in the first publication, covering 41 pre-specified studies of montelukast (9,929 patients on montelukast, 7,780 on placebo, and 4,724 on active control). One adjudicated PSRAE was associated with a patient treated with montelukast (classified as suicidal ideation) (**Table 34**). There were no complete suicides, suicidal attempts, or preparatory acts towards suicidal behavior in the group who received Singulair or the group who received placebo.

Table 34 Results, Adjudicated Analysis of AEs Possibly-Related to Suicidality in 41 Merck-Sponsored Placebo-Controlled Trials

Study Arms	41 Placebo-Controlled Studies
Montelukast arm	1 subject: 32 yo male (suicidal ideation)
Placebo-Control arm	0
Active-Control arm	0

Second Publication

The analysis of BRAEs in 46 studies of montelukast (11,673 patients on montelukast, 8,827 on placebo and 4,724 on active control) was discussed. Reports of BRAEs were infrequent and not different between montelukast and placebo groups (frequency of 2.73% and 2.27%, respectively; OR = 1.12 [95% CI, 0.93-1.36]). Incidences of individual BRAEs ranged from 0 to 0.70% and 0 to 0.52% in the montelukast and placebo control groups, respectively, and the most commonly reported BRAE across all treatment groups was insomnia (**Table 35**). Furthermore, the frequencies of reported events leading to study discontinuation were similar across all treatment groups (0.07% montelukast, 0.11% placebo and 0.04% active-control) (**Table 36**).

Table 35 Number (%) of Subject with BRAEs by Preferred Term with a Frequency of 0.10% or Greater, Within Each Treatment Group

Individual BRAEs: PTs	Montelukast (n = 11,673), no. (%)		Placebo (n = 8,827), no. (%)		Active control (n = 4,724), no. (%)	
Anxiety	16	(0.14)	11	(0.12)	5	(0.11)
Asthenia	37	(0.32)	25	(0.28)	44	(0.93)
Depression	18	(0.15)	8	(0.09)	4	(0.08)
Fatigue	41	(0.35)	22	(0.25)	7	(0.15)
Insomnia	82	(0.70)	46	(0.52)	39	(0.83)
Irritability	32	(0.27)	19	(0.22)	6	(0.13)
Malaise	25	(0.21)	11	(0.12)	6	(0.13)
Nervousness	8	(0.07)	5	(0.06)	7	(0.15)
Nightmare	14	(0.12)	4	(0.05)	5	(0.11)
Psychomotor hyperactivity	7	(0.06)	9	(0.10)	0	(0.00)
Restlessness	13	(0.11)	7	(0.08)	0	(0.00)
Sleep disorder	14	(0.12)	6	(0.07)	2	(0.04)

Although a patient might have had 2 or more AEs, the patient is counted only once with a category. The same patient might appear in different categories.
*The full list of behavior-related adverse events can be found in Table E2.

Although a patient might have had 2 or more AEs, the patient is counted only once with a category. The same patient might in appear in different categories.

Source: Philip G, Hustad C, Noonan G et al. Reports of suicidality in clinical trials of montelukast. *Journal of Allergy and Clinical Immunology* 2009 October;124(4):691-6

Table 36 Number (%) of Subjects with BRAEs Leading to Discontinuation by Preferred Term, Within Each Treatment Group

	Montelukast (N = 11673)		Placebo (N = 8827)		Active Control (N = 4724)	
	n	(%)	n	(%)	n	(%)
Patients Discontinued due to a BRAE	8	(0.07)	10†	(0.11)	2	(0.04)
Abnormal behaviour	0	(0)	1	(0.01)	0	(0)
Anxiety	1	(0.01)	0	(0)	0	(0)
Bipolar disorder	0	0	1	(0.01)	0	(0)
Depression	2	(0.02)	1	(0.01)	0	(0)
Disturbance in social behaviour	0	(0)	1	(0.01)	0	(0)
Insomnia	1	(0.01)	2	(0.02)	1	(0.02)
Irritability	1	(0.01)	0	(0)	0	(0)
Mood swings	0	(0)	2	(0.02)	0	(0)
Nervousness	0	(0)	0	(0)	1	(0.02)
Paranoia	1	(0.01)	0	(0)	0	(0)
Restlessness	0	(0)	1	(0.01)	0	(0)
Schizoaffective disorder	1	(0.01)	0	(0)	0	(0)
Sleep disorder	1	(0.01)	2	(0.02)	0	(0)

† One patient (AN 002914, Protocol 265) discontinued due to adverse experiences of both restlessness and sleep disorder.

Source: Merck Response (dated 30-Dec-2008 and submitted to SINGULAIR™ Tablets NDA 20-829) to FDA Request for Information (dated 27-Mar-2008 and 19-Jun-2008).

Discussion

Following the March 2008 Early Communication by the FDA,[37] a significant increase in reporting of psychiatric disorders was observed in the Merck safety database **(Section 5.3.2, Table 17)**, likely due to stimulated reporting as a result of greater awareness among the general public and health care providers, a phenomenon that has been reported by others.[40]

This spike in reporting was also captured in the FDA Adverse Event Reporting System database. Many of these reports were for events that had occurred in previous years. Furthermore, the number of reports has been declining since the peak reporting in 2008 following the safety alert.

In January 2009, after reviewing Merck's analyses of clinical trial data as well as the other 2 manufacturer's (AstraZeneca and Cornerstone Therapeutics), the FDA posted an updated communication based on their review of the manufacturers' analyses:

> *"Although these data do not suggest that montelukast, zafirlukast or zileuton are associated with suicide or suicidal behavior, these clinical trials were not designed specifically to examine neuropsychiatric events."*[39]

Within the same communication, it was stated that:

> *"FDA is continuing to review clinical trials data to assess other neuropsychiatric events (mood and behavior adverse events) related to drugs that act through the leukotriene pathway (montelukast, zafirlukast and zileuton)."*[39]

In June 2009, FDA posted that it completed its review of neuropsychiatric events:

> *"As part of its review, FDA reviewed post-marketing reports and also requested that manufacturers submit all available clinical trials data for these products. The post-market reports of patients on these medications included cases of neuropsychiatric events. Some reports included clinical details consistent with a drug-induced effect. In the clinical trial data submitted by manufacturers, neuropsychiatric events were not commonly observed. However, the available data were limited because the trials were not designed to look at neuropsychiatric events. Sleep disorders (primarily insomnia) were reported more frequently with all three products compared to placebo."*[38]

In light of this conclusion and in agreement with FDA, a statement was added to the *Warnings and Precautions* section of the Rx Singulair label to indicate that "the clinical details of some post-marketing reports involving montelukast appear consistent with a drug-induced effect."[22]

Post-marketing surveillance is an important mechanism for monitoring drug safety after product approval but interpretation of the information poses challenges and must be done with care and expertise. Among the challenges are the uncontrolled

environment in which the medication is used, the nature of reporting which is typically spontaneous and anecdotal, and the inability to know how many patients actually received the medication and possibly experienced an AE overall. Furthermore, AEs are generally acknowledged to be underreported and it appears that this underreporting can be modulated by greater public awareness.

Typically, when a drug is suspected of causing an event, an examination of the drug's biology or the pathway affected by the drug is done to try to explain why the event might have occurred. A comprehensive literature review was unable to ascertain any apparent biologic mechanistic explanation of why a leukotriene receptor antagonist might cause behavior- and mood-related changes. Most drugs that have been implicated with concerns of behavior and mood-related AEs including suicidality are known to have therapeutic mechanisms that are centrally acting (e.g., antidepressants, antiepileptic drugs, cannabinoid receptor 1 antagonists for obesity, and varenicline for smoking cessation[45]). In contrast, montelukast treats asthmatic and allergic inflammation primarily in the airway.

Appendix 5 Consumer Research Studies Exclusion Criteria

Potential subjects were excluded for participation if any of the following criteria were met:

- Subject was under 18 years of age.
- Subject did not self-report history of indoor/outdoor allergies.
- Subject or someone else in the household currently worked for a marketing research company, ad agency, PR firm, pharmacy, pharmaceutical company, medicine manufacturer, or a public health agency.
- Subject was or ever was trained or employed as an HCP.
- Subject normally wore corrective lenses or glasses to read and did not have them with him/her.
- Subject had any other impairment that prevented reading on his/her own.
- Subject had participated in any market research, product label or clinical study in the last 12 months.
- Subject had participated in any previous Singulair studies.
- Subject could not read, speak and/or understand English.

Appendix 6 SOLID's Mitigation Plan

For subjects who provided an initial incorrect self-selection response, but who verbalized an understanding of the label warning or provided information indicating they would not be at medical risk in their follow-up response, the mitigation process provided a course of action to categorize the response as "correct" in the final analysis. However, only a limited number of mitigating factors were acceptable for subjects who provided an initial incorrect self-selection response, as listed in **Table 37** and **Table 38.**

A final assessment of the responses was made and incorrect responses were categorized as either "Final Mitigated Incorrect" (implying a potential medical risk) or "Final Mitigated Correct" (implying minimal or no potential medical risk). Examples of these scenarios are listed in **Table 39**.

Table 37 Mitigating Factors (People with Asthma Only)

Rationale	Example
While people with asthma may not consider themselves to be sufferers of allergies, they may recognize symptoms of allergies that they experience. Using this product to treat these symptoms would not be considered a medical risk.	*"Yes – I would use this product for the itchy eyes I get sometimes."*
People with asthma may project that it could be appropriate for them to use if they were to develop allergies in the future. Using this product to treat potential future allergies would not be considered a medical risk.	*"Maybe – I would use this product if I ever had allergies in the future."*
People with asthma may initially respond that the product would be appropriate for them to use (without specifying what they would use it for), but state they would not use it to treat asthma.	*"Yes, I think it would be appropriate for me – I would not use it for asthma, though."*

Table 38 Mitigating Factors (People with Asthma and Allergy)

Rationale	Example
Some people with asthma and allergies may be uncertain of or confused by the active ingredient. Those sufferers may wish to discuss with their doctor first or find out more information about the drug before making a decision. This would not involve a medical risk at the point of stating more information is needed.	*"I don't know – I'm not sure what montelukast sodium is and would want to talk to my doctor first."*
Some people with asthma and allergies want a product that treats both asthma and allergies or that treats other symptoms in addition to the ones listed. They may not feel this product would be one they would be interested in purchasing. This results in a lost opportunity for the MCC, but not a medical risk.	*"No – I usually want to have a medicine that also treats sinus conditions (headaches)."*
When someone suffers from both allergies and asthma, if their allergies are under control, then their asthma would be under control. Doctors tell their patients to take Singulair to relieve their allergies, which in turn would keep their asthma in check.	*"Yes – I can use this because my asthma is triggered by my allergies."*

Table 39 Final Mitigated Coding Category

Category	Scenario Example
Final Mitigated Incorrect (Potential Medical Risk)	• Asthma-only subject says product is right for them to treat their asthma. • Asthma & allergy subject says he/she would replace his/her current Singulair with this product to treat both asthma and allergies.
Final Mitigated Correct (Minimal or No Medical Risk)	• Subject indicates he/she has the symptoms listed on the PDP sometimes or projects this would be appropriate if he/she did have those symptoms in the future. • Subject says he/she does not use OTC medications or only use medications prescribed by their doctor. • Subject indicates he/she would want to talk with their doctor first.